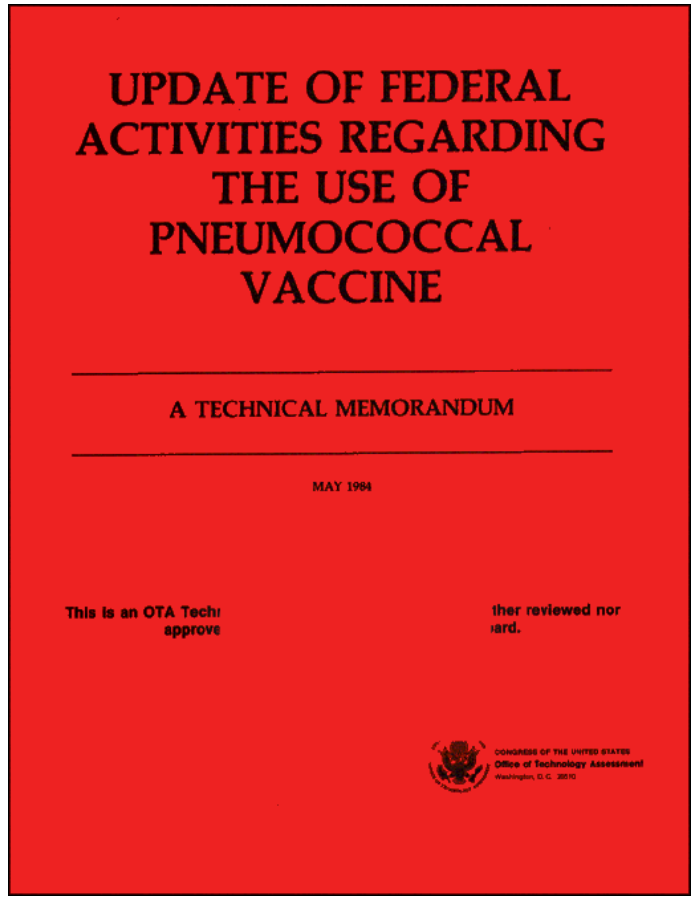
Update of Federal Activities Regarding the Use of Pneumococcal Vaccine

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Preface

The legislation that established Medicare in 1965 excluded from coverage immunizations and certain other technologies used for prevention. In 1981, Congress began coverage of pneumococcal vaccination, but has not extended the same coverage to other preventive vaccines, such as influenza.

In its deliberations regarding pneumococcal vaccine, Congress referred to a 1979 report by the Office of Technology Assessment (OTA) entitled *A Review of Selected Federal Vaccine and Immunization Policies.* This report used the case of pneumococcal vaccine to illustrate policy issues and included a cost-effectiveness analysis. In December 1983, the Subcommittee on Health and Long-Term Care of the House Select Committee on Aging requested OTA to provide current information on the efficacy and safety of pneumococcal vaccine and on Federal involvement in the vaccine's use.

This technical memorandum presents that updated information. The memorandum describes Federal activities that have taken place since 1979; reevaluates the 1979 cost-effectiveness analysis of vaccination against pneumococcal pneumonia, including new information on vaccine efficacy; and discusses policy implications. Although exact data are not available, it is estimated that about 25 percent of people older than age 65 may have received pneumococcal vaccine. The report concludes that, if the Government wishes to promote the use of pneumococcal vaccine, efforts beyond Medicare coverage will be needed to reach elderly adults.

This memorandum benefited from the consultation and review of a large number of persons in the Federal Government, universities, private industry, and medical community (see app. A). Richard K. Riegelman of George Washington University was particularly helpful in evaluating the medical literature. Key OTA staff involved in the preparation of the document were Jane E. Sisk, Elliott Pickar, and Katherine E. Locke.



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Chapter 1

Introduction and Summary

Chapter 1

Introduction and Summary

BACKGROUND AND SCOPE OF THE STUDY

Since 1881 when Pasteur in France and Sternberg in the United States independently isolated the pneumococcus, studies of this bacterium have been associated with pathbreaking discoveries in the sciences of bacteriology and immunology. In 1981, the pneumococcus was also associated with a pathbreaking event in health policy when pneumococcal vaccine became the first preventive technology to be covered by the Medicare Program. According to legislation creating the Program in 1965, Medicare, like most other health insurance, explicitly excluded preventive technologies (e.g., vaccines) from coverage. Although legislation has repeatedly been introduced to cover influenza vaccine, and bills now before Congress would extend coverage to hepatitis B vaccine, to date pneumococcal vaccine remains the only preventive technology covered.

At the time that polysaccharide pneumococcal vaccine[1] was marketed in 1978, the Office of Technology Assessment undertook a study entitled *A Review of Selected Federal Vaccine and Immunization Policies.* Published in 1979, that report used pneumococcal vaccine as a case study and included a cost-effectiveness analysis of the vaccine's use against pneumococcal pneumonia. In December 1983, as an outgrowth of their interest in preventive services for elderly people, the Subcommittee on Health and Long-Term Care of the House Select Committee on Aging requested OTA to update that work. The Subcommittee expressed particular interest in evaluation of the vaccine's efficacy and safety and in Federal activities regarding its use, including experience with Medicare coverage.

In the time allotted for this technical memorandum, it was not possible to totally recalculate OTA's previous cost-effectiveness analysis of pneumococcal vaccination against pneumococcal pneumonia (77). However, the memorandum contains current information about many of the variables in the analysis and an evaluation of the degree to which previous predictions remain valid in light of new evidence. Particular attention is given to the vaccine's efficacy, which has been the subject of some uncertainty in recent years. Familiarity with the earlier report would be helpful because this technical memorandum concentrates on the literature and other developments after 1979.

Although there is great policy interest in compensation for recipients who suffer severe adverse reactions from vaccines, this technical memorandum does not consider that subject. As a polysaccharide (as opposed to a whole killed or attenuated live) vaccine, pneumococcal vaccine has been associated with a low rate of adverse reactions and few severe ones (see ch. 2). In addition, pneumococcal vaccine, unlike many other vaccines, especially those intended for children, is not recommended for general use, and its use in the general population has not been supported with Federal grant funds.

pneumococcal bacteria may cause disease in different parts of the body: pneumonia in the lungs, otitis media in the middle ear, meningitis in the brain, and bacteremia as a blood-borne infection. Although pneumococcal pneumonia is the most common form of pneumococcal disease (58), such a diagnosis is difficult to differentiate from other forms of pneumonia because pneumococcal bacteria exist in the upper respiratory tract without causing disease.

At the time of the OTA report on vaccine policy, two pneumococcal polysaccharide vaccines *were* being marketed, each with capsular polysaccharides of 14 of the 83 pneumococcal types. Merck Sharpe & Dohme began marketing PNEUMOVAX in February 1978, and Lederle Laboratories in-

[1]The vaccine is composed of purified polysaccharides from the capsules of different types of pneumococci. When injected into humans, these capsular polysaccharides stimulate the formation of serum antibodies that provide immunity against those types of pneumococci (77).

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troduced PNU-IMUNE in August 1979 (77). The Food and Drug Administration (FDA) in 1977 had approved the vaccine for immunization against pneumonia and bacteremia caused by the types of pneumococci in the vaccine in certain high-risk people 2 years of age or older. These groups, who were at higher risk of developing complications or dying from pneumococcal pneumonia, were identified as people 50 years or older; people with diabetes mellitus or chronic heart, bronchopulmonary, renal, or metabolic disease; residents of chronic care facilities; or people recovering from severe diseases. FDA also stated that data suggested efficacy for people over age 2 with sickle cell anemia, splenectomy, or impaired splenic function.

In 1978, the Advisory Committee on Immunization Practices (ACIP) (now the Immunization Practices Advisory Committee), a body of nongovernmental experts who advise the Public Health Service, issued recommendations on the use of pneumococcal vaccine (59). The ACIP stated that limited information on efficacy prevented definitive recommendations, but did indicate certain high-risk groups that might benefit from the vaccine. Although the statement noted that incidence and mortality from pneumococcal disease, and presumably the benefits from vaccination, increase with age, it did not indicate a specific age.

The remainder of this chapter summarizes material presented in the body of this technical memorandum on developments that have occurred since 1979 in refinement of the vaccine, recommendations for its appropriate use, and Medicare coverage. Also summarized is the reexamination of the 1979 cost-effectiveness analysis. The chapter concludes with a section on implications for policy.

SUMMARY

Federal Activities

Since 1979, Federal activities regarding pneumococcal vaccine have concentrated on developing a new vaccine with broader coverage of pneumococcal disease and on refining information about appropriate use.

In June and July 1983, the FDA approved for marketing two additional pneumococcal vaccines, each with antigens (polysaccharides) of 23 pneumococcal types. The two vaccines were marketed in July 1983, PNEUMOVAX-23 by Merck Sharpe & Dohme and PNU-IMUNE 23 by Lederle Laboratories. FDA established the 23-valent formulation based on the latest epidemiology and collaborative studies with the two manufacturers. FDA coordinated its activities with the World Health Organization, which adopted the same formulation for international standardization. The 23-valent vaccine contains more stable antigens for some pneumococcal types and provides coverage against 90 percent of the types causing pneumococcal bacteremia. By contrast, the 14-valent vaccine contained types responsible for 75 percent of pneumococcal bacteremia (see ch. 2).

The National Institutes of Health (NIH) and particularly the Centers for Disease Control (CDC) have funded or gathered information on the immunogenicity and efficacy of the vaccine, especially for elderly and other high-risk groups (see ch. 3).[2] The ACIP has used this and other information to reformulate their recommendations. An ACIP statement in 1981 again noted the lack of definitive information on which to judge vaccine efficacy for many high-risk groups, including elderly people. But the 1981 recommendations stated that certain high-risk people "should be considered" for vaccinations or "should benefit" instead of the 1978 language that they "might benefit" (58). In both years, the ACIP noted that mortality from pneumococcal disease increases with age, but did not cite a particular age group as be-

[2] Immunogenicity refers to the production of an immune response, such as the production of antibodies **in response to the antigens in the vaccine. Efficacy is the probability that the vaccine will protect against disease under ideal conditions of use, such as clinical trials. Although a vaccine may also reduce the seventy of disease, the only data for pneumococcal vaccine relate to prevention of disease. Effectiveness refers to the probability of vaccine protection under average conditions of use, such as clinical practice.**

ing at high risk. The ACIP did identify people at high risk of developing pneumococcal disease or having more severe complications because of certain underlying conditions: sickle cell anemia, multiple myeloma, cirrhosis, renal failure, splenic dysfunction, splenectomy, and organ transplant. In addition, people with other chronic conditions may be at higher risk: alcoholism, diabetes milletus, congestive heart failure, chronic pulmonary disease, or conditions associated with immunosuppression. People with cerebrospinal fluid leakage may be at higher risk of pneumococcal meningitis (59).

In light of additional data on the efficacy of the vaccine, the ACIP in February 1984 expressed a much more positive attitude regarding the use of the vaccine (see ch. 2) and stated the intention of reevaluating its recommendations. After a subcommittee report at the April 1984 meeting, the ACIP began to draft a revised statement.

As a result of legislation passed in December 1980, the Medicare Program began covering pneumococcal vaccination as a Part B service on July 1, 1981. Unlike most other Part B services, which are subject to a deductible and copayment by the beneficiary, Medicare pays 100 percent of the reasonable charge for the vaccine and its administration.

No data are available on the use of pneumococcal vaccine by Medicare beneficiaries or expenditures by the Medicare Program for pneumococcal vaccination (see ch. 4). On the basis of sales reported by vaccine manufacturers and different definitions of the target group, 20 to 25 percent of the people over age 65 or as many as 6.6 million Medicare beneficiaries may have received pneumococcal vaccine.

Reconsideration of the Cost Effectiveness of Vaccination Against pneumococcal Pneumonia

OTA's cost-effectiveness analysis calculated the expected changes in health effects and medical care costs produced by vaccination against pneumococcal pneumonia as compared with continuation of the situation before the vaccine was available, in which the disease was treated if it occurred. The analysis first took a societal perspective and included all medical care expenditures, whether paid by patients or third parties. The subsequent analysis included only expenditures that would be paid by the Medicare Program. The base case used estimates of variables that were considered most likely in 1978, and a sensitivity analysis tested the effect on the results of varying the values of certain factors *over* reasonable ranges.

No data were available for this technical memorandum on the current incidence of pneumonia, which has declined substantially over recent decades in all age groups. It is therefore not known whether the use of pneumococcal vaccine has prevented pneumococcal pneumonia to such a degree that the secular decline in pneumonia has been accelerated.

Reconsideration of OTA's analysis confirmed the base case estimates for all the variables except the incidence of pneumococcal pneumonia and the duration of immunity for elderly people. Although most of the information concerned the 14-valent vaccine, available data on the 23-valent vaccine were incorporated as well.

OTA's base case estimated that 15 percent of all pneumonia is pneumococcal, which corresponds to about 2.2 cases per 1,000 U.S. population per year. The low estimate was 10 percent of all pneumonia. Because of the difficulty of distinguishing pneumococcal from other pneumonias, estimates of incidence have been extrapolated from data on the incidence of pneumococcal bacteremia. Data on bacteremia that have been accumulated since 1979 suggest that the rate of pneumococcal pneumonia is closer to the low estimate of 10 percent of all pneumonia or 1.4 cases per 1,000 population per year (see ch. 2). By calculating incidence as a percentage of all pneumonia, OTA's analysis had incorporated the fact that incidence and complications are higher for elderly people.

Although OTA's base case estimate of 8 years duration of immunity from the vaccine continues to apply for healthy adults, it may be somewhat shorter for elderly and chronically ill people. No data relate directly to the duration of immunity that has been observed for these groups; instead, the new information comes from declines in an-

tibody levels over time. For pneumococcal vaccine as for immune responses in general, people with disease causing immune suppression are likely to have much shorter durations of immunity. For most groups, the duration of immunity is likely to be well above OTA's low estimate of 3 years.

With the introduction of the 23-valent vaccine, OTA's base case estimate that pneumococcal vaccine has an efficacy rate of 80 percent continues to appear reasonable (see ch. 2). This conclusion is based on information regarding efficacy that has been reported by the CDC and other investigators. The 14-valent vaccine has been about 65 percent effective in preventing pneumococcal bacteremia in people over age 2, including those who are elderly. On the basis of the increased coverage against pneumococcal types in the 23-valent vaccine, it is estimated that the new vaccine will have an efficacy rate of about 80 percent against pneumococcal pneumonia.

In 1978, OTA estimated that each vaccination cost $11.37, including the vaccine and its administration.[3] The current estimate of $14.65 incorporates a lower vaccine price and higher administration fee. The Medicare Program, which reimburses only for reasonable charges, may pay less than this amount. In one State, for example, Medicare is currently reimbursing $9.60 for a pneumococcal vaccination. The current estimated cost of vaccination under a public immunization program is $3.80, compared with the 1978 estimate of $3.45 (see ch. 2).

If the medical costs of survivors are excluded, OTA's 1978 analysis indicated that pneumococcal vaccination against pneumonia would be cost saving to society for people 65 years or older. **With survivors' medical care costs included,** vaccination was estimated to gain a year of healthy life for an elderly person for $1,000.

With the 1978 base case estimates, but **excluding survivors' medical costs,** vaccination for an elderly person would be even more cost saving in 1983 because treatment costs have risen more than vaccination costs. **Excluding survivors' medical costs** but incorporating the updated assumptions, a lower incidence of pneumococcal pneumonia (10 percent of all pneumonia) and a shorter duration of immunity (3 years), raises the net cost of gaining a year of healthy life. For a person 65 years or older, the net cost would then range from about $300 to $6,200 **per** year of healthy life gained by vaccination against pneumococcal pneumonia (see ch. 2). Continuing research and surveillance will be able to clarify the duration of immunity for elderly people, which has the most effect on these estimates.

The 1978 analysis estimated that the Medicare Program would incur a net cost per elderly beneficiary vaccinated of about $5 for a gain in 1.59 healthy days of life. The results for the Medicare Program parallel those for society except that Program costs **include survivors' medical costs** and do not include all savings in treatment costs (see ch. 2). With the 1978 base case estimates and 1983 costs, including $9.60 as the vaccination cost, Medicare would realize net savings of about $2.40 per elderly beneficiary vaccinated. With $9.60 as the reasonable charge paid by Medicare, a lower incidence of pneumococcal pneumonia (10 percent of all pneumonia), and a shorter duration of immunity (3 years), Medicare would incur net costs of about $5.50 per elderly beneficiary vaccinated or about $4,400 per year of healthy life gained. If 25 percent of elderly beneficiaries were vaccinated (about 6.6 million), the net cost to the Medicare Program over time in 1983 dollars would total about $37 million to gain about 8,400 years of healthy life.

[3] Ideally, a cost-effectiveness analysis measures the actual cost of resources used. **In practice, charges for services, especially for physician services, are often used as a proxy for costs.**

POLICY IMPLICATIONS

As the adoption and use of a medical technology proceed, the evolution and refinement of indications for its use are a common and worthwhile phenomenon. This process is continuing for pneumococcal vaccine with the involvement of NIH, which is funding research to assess vaccine immunogenicity and efficacy; the Veterans Administration (VA), which is supporting a clinical trial; the CDC, which is conducting surveillance activities; and the ACIP, which is reconsidering its recommendations in light of new information.

Uncertainty concerning the duration of immunity and the immunogenicity and efficacy of the vaccine for high-risk groups remains (see ch. 2). It has been estimated that clinical trials to establish vaccine efficacy more definitively would require more than 100,000 people and large research expenditures (69). Alternative, less expensive methods are available and being used, such as retrospective case control studies. Although immunogenicity is only a proxy for efficacy, it would be less costly to reexamine the antibody levels of people in earlier clinical trials. These alternatives would be appropriate for NIH to consider in the context of its grant solicitations. The results of the VA clinical trial of high-risk veterans will bear on both the duration of high antibody levels and efficacy over at least a 3-year period (73). In light of these uncertainties, it is disturbing that the new 23-valent vaccine was not tested on elderly or other high-risk groups before FDA licensed it in 1983.

Approximately 25 percent of the target group has received pneumococcal vaccine since 1978, with a range from 20 to 35 percent, depending on the definition of high-risk groups and the size of inventories. This level of use may appear low considering the health benefits to be gained from greater use and the cost-effectiveness results.

From another vantage point, however, it is surprising that use has reached even this level considering the impediments faced by preventive technologies in general and pneumococcal vaccine in particular. The use of preventive technologies for adults has characteristically been low. Both influenza and pneumococcal vaccines have had low levels of use, even among the patients of physicians who support them (55). Neither adults nor the clinicians who care for them have been attuned to prevention in the way that parents and pediatricians have been for children. The strategies appropriate for preventive technologies for adults may also differ by being targeted to specific high-risk groups instead of to the general population. For childhood immunization, entry to elementary school has served as a review point for vaccination, and the promotion of vaccines for adolescents and young adults has increasingly involved other institutions, such as colleges and the military. It is more difficult to conceive of institutional strategies for older adults.

pneumococcal vaccination has faced additional barriers. Uncertainty has surrounded the efficacy of the vaccine since it was first marketed in 1978, as indicated by the ACIP statements on its use. This situation may well have discouraged clinicians from vaccinating their patients. There is also a low level of public awareness of pneumococcal disease. Elderly people are therefore unlikely to feel at great risk of such disease and to seek the vaccine from their physicians. It is also not clear that clinicians perceive the greater risk of complications for elderly or other high-risk groups.

Because of these general and specific constraints, wider use of pneumococcal vaccine would require that further steps be taken. One is a clearer statement by the ACIP on whether or not the vaccine is recommended for certain high-risk groups, including elderly people. Primarily because of the uncertainty regarding efficacy and the tone of the ACIP recommendations, the CDC has not moved to implement the objective of the Department of Health and Human Services to have 50 to 60 percent of the target population vaccinated by 1990. The ACIP is working on a revised statement, which should be published this year.

If the Government wishes to promote the use of pneumococcal vaccine, efforts beyond Medicare coverage will be needed to reach elderly adults. The hospital may represent an institution through which pneumococcal vaccination could

be provided. On the basis of the percentage of patients with pneumococcal pneumonia or bacteremia who were hospitalized within the previous 3 years for any cause, it has been estimated that vaccinating certain patients on discharge from their previous hospitalization could avoid 10 percent of hospital admissions for all pneumonia (22). Since revaccination poses some hazard (see ch. 2), such an approach would require some precaution so that patients who have already received the vaccine are not mistakenly revaccinated. Since pneumococcal vaccination, unlike almost all other services, is excluded from the new system of payment by diagnosis related groups, Medicare will reimburse hospitals for the cost of vaccinating inpatients (see ch. 4).

Another possible mechanism is providing Federal grant funds for pneumococcal vaccine like those for childhood vaccines. This mechanism has been used for influenza vaccine, another vaccine targeted to specific segments of the population, although only for 1978-79 and 1979-80. The CDC would then administer these grants to States. In contrast to Medicare coverage, which takes a passive stance, this approach sets up at the Federal level a cadre of people interested in promoting vaccine use by working at State and local levels. The cost of vaccination under such public programs is also much lower than under private provision and hence Medicare, an estimated **$3.80** compared with $9.60 or $14.65 (see ch. 2).

Certain measures regarding preventive technologies for adults relate to pneumococcal vaccine. Segments of the medical profession are taking steps to promote the use of preventive technologies by physicians who care for adults. The ACIP has developed detailed guidelines for adult immunization and expects to publish them in CDC's *Morbidity and Mortality Weekly Report* in 1984. The Committee on Immunization of the American College of Physicians is developing guidelines for internists regarding adult immunizations and has coordinated its activities with the ACIP (74). The Committee intends to publish its statement in a medical journal and may channel information into medical schools through the Society for Research and Education in Primary Care and Internal Medicine. Both of these guidelines will include statements on pneumococcal vaccine.

Although special factors apply to pneumococcal vaccine, in many respects it typifies the problems of a preventive technology for adults. With increases in life expectancy, more adults have more years in which to benefit from prevention of disease and disability. As the percentage of the population that is elderly continues to grow, policy issues regarding such preventive technologies promise to take on added importance. More definitive findings about preventive technologies for adults and for the general population, however, would require a more exhaustive study of the literature and public policy than is possible in this technical memorandum.

Chapter 2

Reconsideration of the Cost Effectiveness of Vaccination Against Pneumococcal Pneumonia

Chapter 2

Reconsideration of the Cost Effectiveness of Vaccination Against pneumococcal Pneumonia

A 1979 OTA report on Federal vaccine policy included as a case study a cost-effectiveness analysis of vaccination against pneumococcal pneumonia (77). That analysis calculated the expected changes in health effects and medical care costs produced by vaccination against pneumococcal pneumonia as compared with continuation of the situation before the vaccine was available, in which the disease was treated if it occurred. The results, expressed as cost-effectiveness ratios, represented the net medical cost per year of healthy life that would be gained by a person who was vaccinated.

The analysis first took a societal perspective and included all medical care expenditures, whether paid by patients or third parties. The subsequent analysis from the perspective of the Medicare Program included only expenditures that would be paid by that program. Children under age 2 were excluded because the vaccine has not been shown to be uniformly efficacious for them. A sensitivity analysis tested the effect on the results of varying the values of several uncertain factors over reasonable ranges.

This technical memorandum draws on information accumulated since 1979 to reevaluate several assumptions in that analysis. Also incorporated is information on the 23-valent pneumococcal vaccine which, has been marketed since July 1983. Specifically examined are assumptions regarding the following variables outlined in table 1:

- incidence of pneumococcal pneumonia,
- proportion of pneumococcal pneumonia caused by the types of pneumococci against which the vaccine is directed,
- efficacy rate,
- duration of immunity,
- safety,
- cost of vaccination, and
- medical costs in extended years of life.

This chapter first reexamines the estimates of those variables and then *uses* the revised estimates to reexamine the cost-effectiveness results and the costs to the Medicare Program of paying for pneumococcal vaccination. It was not possible within the confines of this technical memorandum to obtain current information on some of the assumptions made in the cost-effectiveness analysis. No new information was obtained on deaths from all pneumonia cases or on the rate at which mortality from all pneumonia cases is declining. Nor was there a reexamination of the way pneumonia cases are treated, including the extent to which people are treated as inpatients or on an ambulatory basis, the use of diagnostic procedures such as chest X-rays and laboratory tests, and the use of antibiotics. It was also not possible in this technical memorandum to recalculate the sensitivity analysis, with high and low ranges of uncertain variables.

Although discount rates and the weights used for the morbidity-mortality index (quality-adjusted life years or QALYs,) were not specifically reexamined, their values continue to appear reasonable. The discount rate takes into account the preference that people have for obtaining benefits now instead of in the future and the fact that funds can be invested in alternative ways (78). The discount rate, which concerns time, is distinct from inflation, which concerns the level of prices. OTA's cost-effectiveness analysis expressed all costs in terms of 1978 dollars. Although it was not possible to reexamine the use and price of treatment for *pneumonia, the* section on the cost of vaccination reviews changes that have occurred in the relative prices of hospital and physician services.

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Table I.–Assumptions for OTA's Base Case and Sensitivity Analysis,[a] 1978

Variables	Base case	Sensitivity analysis[a] High	Low
Proportion of pneumonia that is pneumococcal	15%	35%	10%
Deaths from pneumonia	Death certificates with pneumonia as the underlying cause	Death certificates with pneumonia mentioned	Base case estimate
Decline in mortality from pneumonia	Same decline as overall death rate	Fast decline[b]	No decline
Cases of inpatient pneumonia	First listed diagnoses of pneumonia from Hospital Discharge Survey	All listed diagnoses of pneumonia from Hospital Discharge Survey	Base case estimate
Cases of ambulatory pneumonia	Based on pneumonia visits from National Ambulatory Care Survey and adjusted data from Health Interview Survey	Based on data from Health Interview Survey	Base case estimate
Proportion of pneumococcal pneumonia caused by vaccine types	75%	100%	500/0
Efficacy rate	800/0	100%	40%
Duration of immunity	8 yrs.	72 yrs. (lifetime)	3 yrs.
Safety:			
General side effects	1 case of severe systemic reaction per 106,000 vaccines, 5 cases of fever per 100 vaccines	Base case estimate	Base case estimate
Guillian-Barré syndrome as side effect	No incidence	Incidence same as with 1976 swine-flu vaccination	Base case estimate
Cost of vaccination	$11.37	Base case estimate	$3.45
Medical costs in extended years of life	Included	Base case estimate	Base case estimate
QALY weights for disability days	Day in bed 0.4; day out of bed 0.6	Day in bed $\sqrt{0.4}$; day out of bed $\sqrt{0.6}$	Day in bed 0.4^2; day out of bed 0.6^2
Discount rate	5%	10%	0%

[a]For some variables, the reasonable range of values was bounded by one alternative value, and fOr other variables, by two alternative values.
[b]Implied elimination of 97 percent of pneumonia deaths within 40 Years.

SOURCE: J. S. Willems, C. R. Sanders, M. A. Riddiough, and J. C. Bell, "Cost Effectiveness of Vaccination Against pneumococcal Pneumonia," N. *Engl. J.* Med. 303(10):553-559, Sept. 4, 19S0.

The QALY weights to calculate the morbidity-mortality index were used only to illustrate the effect on the results of different values (77). An implicit assumption is made that continued life is preferable to death, an assumption that seems reasonable for a fairly short acute illness, such as pneumonia.

In an evaluation of the efficacy of pneumococcal vaccination against pneumonia, several clinical points should be kept in mind. The pneumococcal bacteria may cause disease in different parts of the body: pneumonia in the lungs, otitis media in the middle ear, and meningitis in the brain. An infection may spread from one of the local sites

to a bacteremic or blood-borne infection. Pneumococcal vaccine contains the types of pneumococci most likely to cause pneumococcal bacteremia, a severe disease with a high incidence of death and disability. But the pneumococcal types frequently causing bacteremic disease maybe different from the types responsible for local infections. Thus, vaccination may not reduce the incidence of pneumococcal pneumonia by so high a percentage as pneumococcal bacteremia. The reduction in bacteremic disease, however, may disproportionately reduce morbidity and mortality and may reduce the severity of infections that would otherwise progress to bacteremia.

pneumococcal pneumonia is the most common form of pneumococcal disease. pneumococcal pneumonia can be a severe form of pneumonia frequently worse in terms of morbidity and mortality than other community-acquired pneumonias. The diagnosis of pneumococcal pneumonia is difficult since the pneumococcal organism may be carried in the upper airways without producing pneumonia. As a result, culture of the organism does not always indicate that the pneumococcus is the cause of a pneumonia case.

Three different concepts relate to protection against disease and, specifically, the protection that pneumococcal vaccine confers against pneumococcal pneumonia. The efficacy of a vaccine is considered to be the probability that it will protect against disease under ideal conditions of use, such as those in clinical trials. Although a vaccine may also reduce the severity of disease, the only data for pneumococcal vaccine relate to disease prevention. Immunogenicity refers to the production of an immune response, in this case the production of antibodies in response to the antigens in the vaccine. Antibody levels may be an indicator of protection against pneumococcal disease, but are not conclusive evidence. Despite certain antibody levels, a person may not be protected against disease if other components of the immune system are not operating normally. Conversely, a person maybe protected in spite of low rises in antibody levels. Effectiveness, the third concept, refers to the probability of protection against disease, but under average conditions of use, such as that of clinical practice.

INCIDENCE OF pneumococcal PNEUMONIA

OTA's cost-effectiveness analysis assumed that **15** percent of all pneumonia was pneumococcalo This percentage was assumed to be constant for all age groups. OTA estimated that in 1978 there were 3.2 million cases per year of pneumonia in the United States (77). For the 1978 U.S. population of 222.6 million (80), OTA's assumption for the base case is tantamount to an annual incidence of approximately 2.2 cases per 1,000 population. The low estimate assumed that 10 percent of pneumonia was pneumococcal or about 1.4 cases per 1,000 population.

The actual incidence of pneumococcal pneumonia still remains uncertain. The vaccine recommendations of the Immunization Practices Advisory Committee (ACIP) provided a broad range of estimates from **0.68** to 2.6 cases per 1,000 population per annum (58). Three different methods for estimating incidence of pneumococcal disease have been used. Estimates at the low end of this range are based on recent studies of pneumococcal isolates of blood and cerebrospinal fluid from studies of entire communities. Estimates at the upper end of the range were obtained from selected populations using respiratory secretions of patients with and without pneumonia.

Mufson, et al. (54), conducted a prospective study of blood and cerebrospinal fluid from individuals admitted to hospitals providing 80 percent of the beds for a population base of 300,000 in Huntington, W. Va., and surrounding counties. They found an overall bacteremia rate of 7.5 cases per 100,000. This overall rate was similar to rates obtained by Filice, et al. (24), of 8.5 cases per 100,000 population in a retrospective study in Charleston County, S.C.

The studies of bacteremia do not provide a direct incidence of pneumococcal disease unless one

knows the percentage of pneumococcal disease that becomes bacteremic. In addition, these studies may underestimate the incidence of pneumococcal disease because not all patients with pneumococcal disease receive blood cultures, and prior antibiotic therapy rapidly renders blood cultures negative. In addition, studies of bacteremia do not provide an adequate assessment of the effects of meningitis due to pneumococci.

Conversion of bacteremic data to pneumococcal incidence data requires an assumption about the percentage of pneumococcal disease that becomes bacteremic. Older estimates assumed that **20** to **30** percent of cases of pneumococcal pneumonia developed bacteremia. Recent studies (5,8,50) have found rates of bacteremia below 20 percent. The newer estimates of bacteremia may reflect a lower rate of bacteremia among those who seek or are provided care early in the course of their disease.

In applying these lower estimates of the percentage of individuals who develop bacteremia, one obtains rates of pneumococcal disease consistent with the low end of the ACIP incidence estimates.

Incidence rates at the high end of the range are based on studies at selected sites. Estimates from health maintenance organizations (HMOs) provide data on populations not necessarily at high risk or high incidence of pneumococcal pneumonia. According to Austrian's data from the Kaiser-Permanente Medical Care Program, San Francisco area enrollees over age 45 had an annual rate of about 1.5 cases of pneumococcal bacteria per **1,000** population **(5).** Patrick and Woolley **(56)** found a rate 2.3 cases per 1,000 population among about 10,000 patients 18 years and older at the Salt Lake City Family Health Program, a staff model HMO. Despite efforts to carefully define pneumococcal pneumonia, these studies may overestimate the frequency of pneumococcal pneumonia since, as mentioned earlier, pneumococci are frequently carried in the upper airways without being the cause of pneumonia.

A third method of estimating the incidence of pneumococcal pneumonia relies on isolates of pneumococci from the throats of those with pneumonia v. control individuals. These studies develop measures of attributable risk. Fey, et al. **(25),** used this method to estimate a rate of 1.3 cases per 1,000 population among patients at Group Health Cooperative, a 'prepaid group in Seattle. But as David Fraser formerly of the Centers for Disease Control (CDC) noted, the "delicate balance" of the bacterial flora of the throat "can be tipped by the use of antibiotics or the occurrence of various infections" (77). This situation renders questionable the meaning of the presence or absence of pneumococcus in the upper respiratory systems of people with and without pneumonia.

The American College of Physicians in their Clinical Efficacy Assessment Project concluded that overall incidence probably lies between the higher and lower estimates, in the range of 1 to 2 annual cases per 1,000 population per year (67).

In an evaluation of incidence data, it is important to remember that all available studies indicate a considerably increased incidence of pneumococcal pneumonia and bacteremia among elderly people. The population-based bacteremia data of Mufson, et al. (54), and Filice, et al. (24), suggest that the rate for those older than age 60 is more than two times the overall rate (with no control for confounding medical conditions) and that elderly people are more likely to die if they experience pneumococcal bacteremia.

In summary, the overall incidence rate of pneumococcal pneumonia probably approximates the rate of **1.4** cases per **1,000** population used as the low estimate in OTA's cost-effectiveness study.

PROPORTION OF pneumococcal PNEUMONIA CAUSED BY THE pneumococcal TYPES IN THE VACCINE

OTA's base estimate relied on data from Austrian, Fey, and Valenti suggesting that the 14-valent vaccine would be directed against the pneumococcal types causing 75 percent of the cases of pneumococcal pneumonia. This estimate in turn depended on additional assumptions, which are evaluated below:

1. The distribution of types of pneumococci occurring in bacteremia and meningitis would resemble that occurring in pneumonia.
2. The use of the vaccine would not result in a significant shift of pneumococcal types causing infections.
3. For those pneumococcal types with two or more subtypes, use of the most frequent subtypes would provide good cross protection against the other subtypes.

Assumption 1: The distribution of types of pneu**mococci occurring in bacteremia and meningitis would resemble that occurring in pneumonia.**

Because of the difficulty of acquiring reliable data on the frequency of pneumococcal types and subtypes that cause pneumococcal pneumonia, selection of vaccine antigens and evaluation of the frequency of disease have been based on bacteremia and meningitis data. This situation may represent a significant limitation in formulating the vaccine and evaluating its efficacy and effectiveness against pneumococcal pneumonia.

Bentley, et al.'s, study (8) of institutionalized elderly patients found that the majority of the pneumococcal disease among those not vaccinated (as well as those vaccinated) was due to types not included in the 14-valent vaccine. This observation may have been attributable to the high percentage of vaccinated patients or may have reflected a preexisting tendency for nonvaccine types to cause pneumonia. The data from surveillance at Dorothea Dix Hospital (67) before introduction of the vaccine showed that 80 percent of the bacteremic cases but only 43 percent of all pneumococcal isolates from patients with pneumonia were included in the 14-valent vaccine. Thus, it seems that the pneumococcal types included in the vaccine on the basis of frequency data from bacteremia and meningitis may not accurately reflect the frequency of types causing pneumonia.

Relying on data from blood and cerebrospinal fluid isolates, one cannot expect to include in the vaccine so high a percentage of the types of pneumococci causing pneumonia as was assumed in OTA's cost-effectiveness analysis. Because people with bacteremic disease have much higher mortality (4), it is still worthwhile to direct the vaccine against the types that most frequently cause bacteremia.

Knowledge of the frequency of isolates, the cross-reactivity of subtypes, and the stability of constituents have allowed the formulation of the 23-valent vaccine, whose components should be directed against almost 90 percent of the worldwide isolates from the blood and cerebrospinal fluid. With the same criteria, the 14-valent vaccine covered between 70 and 80 percent of the isolates. Again, only blood and cerebrospinal fluid specimens were used to assess the frequency of pneumococcal disease. The increased number of types included in the 23-valent vaccine are expected to provide increased protection against pneumococcal pneumonia as well, but at present no data confirm or refute this expectation.

Assumption 2: **The use of the vaccine would not result in a significant shift of pneumococcal types causing infections.**

The CDC has acquired evidence regarding stability of the distribution of types of pneumococci causing bacteremia despite the use of the vaccine (12). Since 1978, the CDC has collected approximately **2,500** pneumococcal blood and cerebrospinal fluid isolates from 37 hospitals in 22 States. These isolates show *no* evidence of a shift of pneumococcal types among vaccinated and unvaccinated patients at the current level of utilization of the vaccine.

Assumption 3: For those pneumococcal types with two or more subtypes, use of the most frequent subtypes would provide good cross protection against the other subtypes.

Data on the degree to which one subtype provides cross coverage against another have been acquired as a result of a worldwide surveillance system and studies conducted in preparation for the 23-valent vaccine (62). Most of the work on cross-reactivity has been directed at selection of new subtypes for inclusion in the 23-valent vaccine. These data, however, suggest that the subtypes included in the 14-valent vaccine have not always provided adequate cross-over protection against the other subtypes.

In summary, the 14-valent vaccine could be expected to cover almost 75 percent of the types of pneumococci causing bacteremia but may not cover 75 percent of the types causing pneumococcal pneumonia. OTA's low estimate of 50 percent would appear to more accurately reflect the coverage against pneumococcal pneumonia provided by the 14-valent vaccine. This may underestimate the health benefits, however, since a vaccine directed against bacteremia and meningitis should disproportionately reduce death and disability. Since the 23-valent vaccine covers types that cause 90 percent of bacteremic cases, the new vaccine may also cover a higher percentage of the types responsible for pneumococcal pneumonia as well. However, there are no studies that bear directly on pneumococcal pneumonia.

EFFICACY RATE

OTA's base case estimated that the 14-valent vaccine would be **80** percent effective in clinical practice against the types contained in the vaccine. Since 1979, additional information has been accumulated on the responses to the vaccine of high-risk people with chronic diseases, the responses of people with impaired immune systems, the responses of elderly people, and simultaneous use with influenza vaccine.

Most of the data on antibody response to the vaccine are based on levels of total antibody assessed by radioimmunoassay. Absolute levels required for protection have not been definitively determined, but levels below 300 ng antibody nitrogen/ml are not generally considered protective (45). Many studies report successful vaccination based on a doubling of the antibody levels. For individuals who double their antibody levels from low preexisting levels but fall under 300 ng antibody nitrogen/ml, questions of efficacy remain.

Antibody Responses of High-Risk Groups With Chronic Disease

The short-term antibody response of patients with sickle cell disease, renal disease, diabetes, and chronic obstructive pulmonary disease have been investigated. These diseases are believed to predispose people to pneumococcal disease or to cause increased mortality if it develops **(58).**

Sickle cell patients over 2 years of age have been shown to have a generally adequate antibody response **(l).** Unfortunately, responses, especially to certain pneumococcal types, have not been uniform for those under 2 years of age in whom a large proportion of the pneumococcal disease among sickle cell patients occurs. Sickle cell patients appear to respond suboptimally to type **6** pneumococcal antigen (7), and clinically, cases of type **6** bacteremia have been observed despite vaccination.[1] For most pneumococcal types tested, sickle cell patients over age 2 produce a twofold or greater increase in their antibody levels and are probably protected (7).

The situation for renal disease patients must be separated into the response of those in renal failure, those on dialysis, and those who have undergone transplantation with immune suppression. Cosio, et al. (18), have shown that renal failure patients respond poorly and dialysis patients re-

[1]**This situation is not specific to children with sickle cell disease; many children do not make antibodies to certain pneumococcal types until age 6 to** 10. **Conjugated vaccines (see ch. 3) are being developed to address such problems (4).**

spend quite well. Renal transplant patients respond less than dialysis patients, but the majority reached adequate short-term levels of protection. Thus, assuming that most patients with renal disease can be vaccinated while on dialysis or before renal failure develops, one can assume that protection in renal disease is quite good. Linnemann, et al. 's, study (49) agrees with these findings.

Davis, et al. (19), have demonstrated good short-term antibody responses in chronic obstructive pulmonary disease and Lederman, et al. (47), have demonstrated similar data for diabetes. Thus, there is reason to believe that those with chronic diseases not associated with immunosuppression will be able to obtain effective protection from the vaccine, at least in the short-term.

Antibody Responses of Immunocompromised People

In contrast, patients with diseases causing immunological suppression have been shown to have a poor response to the vaccine. Hosea, et al. (34), demonstrated poor antibody responses among splenectomized patients, but found that the pattern of antibody response paralleled that of normal volunteers in terms of height and rate of increase. Schmid, et al. (64), found a similar pattern of poor response among those with multiple myeloma. The ability of myeloma patients to increase their low preexisting levels of antibodies caused them to recommend pneumococcal vaccine for myeloma patients despite their suboptimal responses.

Patients with Hodgkin's disease have been shown by Siber, et al. **(72),** and Ammann, et al. (2), to have a good response to vaccine before treatment. Antibody levels, however, decrease during subsequent therapy proportionally to the intensity of the therapy. Higher levels of antibodies are present in immunized v. nonimmunized Hodgkin's disease patients, and vaccine is recommended 2 weeks *or more* prior to beginning therapy.

Thus, it appears that individuals with a disease or undergoing therapy that impairs their immunological response have lower levels of antibodies and may well have substantially reduced protection from the vaccine.

Antibody Responses of Elderly People

Antibody responses for elderly people who are currently free of chronic disease have been assessed. For antigen types 3 and 8, Ammann and his colleagues found that elderly individuals had lower baseline levels of antigens, but usually responded with a greater than twofold increase in their antibody titers (3). Hilleman, et al. (31), cite similar data for five pneumococcal types. Immediate post-immunization antibody titers were generally above the 300 ng antibody nitrogen/ml levels considered protective.

Bentley, et al. (9), studied the antibody response of elderly individuals to 11 pneumococcal antigens contained in the 14-valent vaccine. For most types, the post-immunization levels were above the 300 ng antibody nitrogen/ml level even among those over age 80. Low prevaccine antibody levels, reduced response to vaccine, and decline in titer over the subsequent year left many elderly, especially those over 80, with levels below those considered protective at 1 year.

Use With Influenza Vaccine

Use of pneumococcal vaccine simultaneously with influenza vaccine has been studied in terms of antibody levels and side effects (31,51). The levels of antibody after simultaneous use were nearly as high as when each vaccine was used alone. There was only a minimally greater frequency of side effects compared to the use of pneumococcal vaccine alone.

Comparison of Antibody Levels

Comparisons of relative antibody levels among groups are complicated by different methods of detecting, reporting, and combining the antibody levels from individual pneumococcal types. A standard method of comparison has recently evolved. This method uses the geometric mean antibody levels and combines these levels from individual types to obtain an overall Grand Mean antibody level. This method permits comparisons among groups, but does not allow a direct estimate of the efficacy rate. It can be presumed, however, that when the Grand Mean is less than 300 ng antibody nitrogen/ml, a majority of antibody

levels will be below those adequate for protection. The short-term efficacy rate should increase as the Grand Mean increases.

Reported geometric mean or Grand Mean levels for selected groups are as follows:

- **Healthy adults: 834** ng antibody nitrogen / ml (47) to 2,344 ng antibody nitrogen / ml (3).
- **Elderly: 537** to 912 ng antibody nitrogen / ml (3).
- Diabetics: 1,009 ng antibody nitrogen / ml (47).
- Chronic obstructive lung disease: 662 ng antibody nitrogen / ml (19).
- Hemodialysis: 592 ng antibody nitrogen / ml (49).
- Multiple myeloma: 91 ng antibody nitrogen / ml **(45).**

Thus, the data from individual groups suggest only a slight reduction in immunogenicity among most groups at increased risk of pneumococcal disease or those at risk of increased mortality if the disease develops. Individuals with immunosuppression, however, are an exception, with evidence suggestive of poor antibody response even in the short term.

Assessing Vaccine Efficacy

In assessing the clinical use of pneumococcal vaccine, one must distinguish between measures of antibody levels and clinical protection against disease. Clinical effectiveness against pneumococcal disease is the end point that one wishes to measure.

Clinical studies to assess the overall efficacy of the vaccine are hampered by the lack of reliable data on the incidence of pneumococcal pneumonia and the extremely large numbers of people that would be required for a controlled clinical trial, except in high-risk groups. Because of relatively low incidence rates, studies in healthy elderly people would require large numbers.

A controlled clinical trial utilizing the 14-valent vaccine is currently underway as a cooperative study among five Veterans Administration Medical Centers. The study, which began in 1981 and will continue through 1985, has enrolled almost **2,300** patients considered at high risk because of at least one of the following characteristics: age 55 years or older; chronic renal, liver, cardiac, or pulmonary disease; alcoholism; or diabetes mellitus. This trial is the only current randomized prospective study designed to assess the efficacy of the 14-valent vaccine. Although the study is expected to provide information on efficacy in these high-risk people as a whole, the number of people in the trial is probably not sufficient to indicate efficacy for elderly people or other high-risk groups separately. (The study will also develop information on adverse reactions to the vaccine and distribution of pneumococcal types) (73).

The CDC (12,13,15) has developed a retrospective method of assessing efficacy that does not require data on the incidence of pneumococcal disease. This method compares the frequency of type-specific isolates from blood and cerebrospinal fluid among vaccinated and unvaccinated patients. It thereby assumes that without the vaccine, different populations would have the same distribution of pneumococcal types and that the vaccine itself leads neither to a shift in types in the unvaccinated group nor a change in the incidence of disease caused by nonvaccine types in the vaccinated group. Since the method utilizes isolates from blood and cerebrospinal fluid, it does not directly assess efficacy against pneumococcal pneumonia.

The CDC has collected almost 200 pneumococcal blood isolates from individuals who have received the vaccine and over 1,000 pneumococcal blood isolates from individuals who have not received the vaccine. The data suggest that the efficacy of the vaccine for type-specific bacteremia for those over 2 years of age is in the range of **60** to **70** percent. Those older than age **60** had a clinical effectiveness rate similar to the rate for those under **60 (12).** Because of the relatively small number, confidence intervals are still large (10).

The CDC has also assessed efficacy for people with conditions that predispose them to complications, including death, from pneumococcal infection. Included are sickle cell disease, splenectomy, nephrotic syndrome, renal failure including those on dialysis, multiple myeloma, and cirrhosis of the liver. Based on comparatively small numbers

that result in wide confidence intervals, the CDC estimate of efficacy for these groups overall is about 35 percent **(10,12).**

Shapiro and Clemens (69) have applied retrospective case-control study methods to the assessment of vaccine efficacy and obtained efficacy rates very close to the CDC's estimates. Shapiro and Clemens matched 90 cases of systemic pneumococcal disease with individuals of similar age and indications for pneumococcal vaccine. Their overall estimate of efficacy was 67 percent with a similar rate for those over 55 years of age.

The new 23-valent vaccine contains antigens that attempt to protect against all types in which multiple antibiotic resistance has been reported. Increased knowledge about stability of individual antigens has been used to select a subtype antigen (type 6B) to replace a previously unstable antigen (type 6A) for one of the common pneumococcal types. It is hoped that this change will increase the clinical effectiveness of the vaccine against type 6 pneumococcal infections.

Despite the increased number of antigens, the total dose of antigen in the 23-valent vaccine is actually less than in the 14-valent since 25 µg of each antigen is used instead of 50 µg. The reduced dosage of each antigen has not been tested on the elderly, the chronically ill, or the immune suppressed. Despite its adequacy in immunogenicity studies for producing antibody levels among healthy adult volunteers, there is insufficient evidence to assure its adequacy in the groups most likely to need or benefit from the vaccine.

The studies of cross-reactivity regarding the 23-valent vaccine have demonstrated that for selected types the rabbit sera data do not correlate well with human data. Only limited human data were available to assess cross-reactivity. Thus, the estimates of potential efficacy may somewhat overestimate the clinical effectiveness.

In assessing the overall efficacy of the vaccine, one must recognize that pneumococcal vaccine is in fact composed of multiple vaccines (i.e., 14 for the 14 valent and 23 for the 23 valent). Even if each of the individual vaccines has 99 percent efficacy, the overall vaccine would have a substantially lower overall efficacy. For instance, if each of the 14 vaccines in the 14-valent vaccine had 99 percent efficacy, the overall rate would be less than **87** percent **(4).**

In summary, the overall efficacy of the 14-valent pneumococcal vaccine for the pneumococcal types included in the vaccine has been found to be lower than the 80 percent efficacy rate used in OTA's base case. The overall efficacy rate against bacteremic disease is probably between 60 and 70 percent. The rate for those older than age 60 is also consistent with this rate. Those with diseases associated with immune suppression that predispose them to pneumococcal pneumonia have substantially reduced efficacy rates. Since these efficacy rates are based on data from pneumococcus isolated from the blood, it is likely that the efficacy rate of the 14-valent vaccine against pneumococcal pneumonia is somewhat lower because of the probable disparity between types of pneumococcus causing pneumonia and the types which predispose to bacteremia.

There is reason to hope that with the 23-valent vaccine, the overall efficacy rate will increase to close to 80 percent of bacteremic disease among people older than age 2. This figure is derived by direct extrapolation with the following assumptions:

1. Elderly, chronically ill, and high-risk people will respond as well to the 23-valent vaccine as to the 14-valent vaccine.
2. The 14-valent vaccine provides coverage against 75 percent of the pneumococcal types causing pneumococcal bacteremia.
3. The 23-valent vaccine provides coverage against 90 percent of the pneumococcal types causing pneumococcal bacteremia.
4. The 14-valent vaccine has an effectiveness rate of **65** percent against pneumococcal bacteremia among those older than 2 years of age.

Under these assumptions, the expected efficacy rate with the 23-valent vaccine would approach the 80 percent rate used as OTA's base estimate in the cost-effectiveness analysis.

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DURATION OF IMMUNITY

OTA's base case assumed an average 8-year immunity provided by the vaccine. This figure was based on data from previous vaccines tested by Heidelberger in the 1950's (77). There are no data to challenge this assumption among young healthy adults. Mufson's data (53) confirmed the persistence of adequate antibody levels for at least 5 years. Hilleman, et al. (31), presented data on 11 of the types in the 14-valent vaccine suggesting that beyond 2 years, levels of antibody remain relatively stable in normal adults.

Elderly individuals and those with chronic diseases not causing immune suppression tend to have a lower level of antibodies after vaccination. Bentley, et al. (9), have demonstrated that during the 12 months after vaccination, the rate of decline in antibody levels among the elderly tends to parallel those of young individuals. The lower post-immunization levels for the elderly, however, left many elderly with 1 year antibody levels below the 300 ng antibody nitrogen/ml level considered protective. This effect was most evident for those over 80. Preliminary data on dialysis patients (18) suggest that the level of antibody may decline at a rapid rate. It should be expected that the duration of protection for elderly and chronically ill people without immunosuppressive disease will be shorter than the estimate of 8 years for healthy young adults.

For patients at high risk of pneumococcal disease due to immune suppression, such as renal transplant patients, multiple myeloma patients, and patients undergoing immune suppressive therapy for cancer, the response to the vaccine is poor and the duration of protection maybe very brief (45). Of course, such people have generally impaired immune responses that extend beyond pneumococcal infection or pneumococcal vaccine. In addition, children who have their spleens removed for hereditary spherocytosis (a disease affecting the shape and survival of the red blood cells) or after trauma have been shown to have a rapid rate of decline of their antibodies during the first year after vaccination (28). Thus, patients whose immune system is impaired by immune suppression or removal of the spleen may have a reduced duration of protection. Consideration of revaccination of these patients requires further evaluation. At the present time, it seems appropriate to conclude that the duration of protection afforded by the vaccine to these high-risk, low-protection patients is lower than for healthy, young vaccinees.

The effect of lower doses of the antigens in the 23-valent vaccine on the duration of antibody levels is unknown. If the duration of adequate antibody levels is reduced in elderly and immunosuppressed people using the 50 µg dose, there may bean even shorter duration of effective immunity produced by the 25 µg doses of the 23-valent vaccine.

On the basis of very preliminary data, elderly and chronically ill people without immunosuppressive disease most likely have a duration of immunity between 3 years (OTA's low estimate) and 8 years (the base case estimate).

SAFETY: SIDE EFFECTS

Recent data based on experience from the first 4 million doses of pneumococcal vaccine distributed have helped clarify the side effects of the 14-valent pneumococcal vaccine:

- Local reactions are frequent with local redness developing in approximately 30 percent of vaccinees, local discomfort in 40 percent, and local swelling in up to 3 percent. Those reactions are self-limiting (67).
- Three to seven percent of vaccinees develop a mild fever of 1 to 2 days duration (67).
- Approximately 1/100,000 vaccinees develop high fever and generalized symptoms that are also self-limiting (58).
- Three cases of possible anaphaylaxis have been reported among the first 4 million doses distributed (67).
- The American College of Physician's Clinical Efficacy Assessment Project found that

no cases of Guillain-Barré syndrome have been reported as of 1982 (67). The Food and Drug Administration does indicate that Guillain-Barré syndrome has rarely been reported in temporal association with pneumococcal vaccine, but that no cause and effect relationship has been established (82).

- The ACIP does not recommend the vaccine for use during pregnancy "unless the risk of infection is substantially increased" **(58).**
- Local and systemic reactions are more frequent when revaccination occurs within 5 years. The ACIP recommends against revaccination of adults **(58).** Vaccine manufacturers also recommend against revaccination.
- Adults of blood group O or B immunized with pneumococcal vaccine manufactured by Merck Sharpe & Dohme prior to 1980 responded with an elevation of their anti-A antibodies. This reaction had the potential for inducing hemolytic disease of the newborn. The substance causing this response was found to be an impurity and was removed from subsequent vaccines. This episode does illustrate the potential for unpredictable side effects of current and future vaccines (62).
- Two patients with thrombocytopenia have been reported to have relapses after receiving the vaccine (43).
- Theoretical concerns that existed about vaccinating individuals with autoimmune diseases have not been substantiated in studies of Sjogren's syndrome (42) or systemic lupus erythematosus (39). No evidence of reduced renal function resulting from deposition of antigen-antibody complexes has been observed (42).

OTA's cost-effectiveness analysis assumed an incidence of fever of 5 cases per 100 vaccinees and an incidence of severe systemic reactions of 1 case per 100,000 vaccinees. The base case estimate of Guillain-Barré syndrome was zero. These estimates correspond closely to those subsequently observed in clinical practice.

Local reactions are related to total dose, and severe reactions on revaccination may be related to antibody levels. Since the total dose of **23**-valent vaccine contains fewer micrograms than the 14-valent one (575 v. 700 µg), the potential for adverse reactions is expected to be the same or less than with the 14-valent vaccine.

Revaccination of patients who have received the 14-valent vaccine with the 23-valent vaccine is contraindicated due to the higher frequency of severe local and systemic reactions that has been observed with booster doses **(82).** If the 23-valent vaccine proves substantially more effective than the 14-valent one, a new preparation will be required to deal with this problem.

COST OF VACCINATION

For OTA's base case with costs expressed in **1978** dollars, vaccination by a private physician was expected to cost $11.37, **$4.90** for the vaccine and **$6.47** for the physician's fee to administer the injection.

For this technical memorandum, costs were recalculated in 1983 dollars. Until December 1983, both manufacturers of pneumococcal vaccine continued to list the price of 5-dose vials at $24.50 or $4.90 per dose. The price was then raised 8 percent to $26.50 or $5.30 per dose. Since 1979, most sales (about 80 percent) have been at discounts averaging about 20 percent off the list price. With such a discount, the average price charged at the end of 1983 was $4.43, an actual decrease of 9 percent over the 1978 price.

From 1978 to 1983, the Consumer Price Index for physician services increased 57.9 percent (38). If the injection fee increased at that rate, it would have reached $10.22 in 1983. The 1983 estimate for the total cost of vaccination is therefore $14.65 per person, an increase of 28 percent over the 5-year period, entirely because of the increased injection fee.

The important cost consideration in reexamining the assumptions of the cost-effectiveness analysis is the relative cost of preventing pneumococ-

cal pneumonia through vaccination versus the cost of treating the disease if it occurs. The 1978 analysis, which expressed all costs in constant 1978 dollars, projected through 2050 the medical care costs that would be incurred with and without vaccination. Although the specific costs of treating pneumonia in 1983 have not been derived, the per capita costs of medical care and especially hospital care have risen much more rapidly than the cost of pneumococcal vaccination. From 1978 through 1983, the medical care component of the Consumer Price Index rose 62.9 percent and the index for hospital and other medical services rose 82.6 percent (38). As noted above, the price index for physician services rose more slowly than for hospitals.

It is possible that reductions in the extent to which pneumonia patients were hospitalized, in their lengths of stay, or in their inpatient or ambulatory use of diagnostic tests could have offset these price rises. From 1964 to 1971, for example, the number of laboratory tests and X-rays fell for an ambulatory pneumonia patient (68). But during that period, use of these same services rose for a pneumonia patient treated in a hospital as an outpatient or an inpatient. More information is needed to determine whether or not changes in technology use offset all or part of the price increases from 1978 to 1983.

OTA's cost-effectiveness analysis included as a low estimate of vaccination cost an estimate of the cost under a public immunization program ($2.45 for the vaccine and $1.00 for its administration). In 1983 dollars, the estimated cost would be $3.80 ($2.22 for the vaccine and $1.58 for its administration), a sum substantially lower than private provision.

As noted in chapter 4, each Medicare carrier establishes its own reasonable and customary charge that it will reimburse for a pneumococcal vaccination given to its beneficiaries. At least one State carrier in January 1984 was paying $9.60 for the vaccine ($7.50 for the vaccine and $0.10 for the syringe) and its administration ($2.00), a figure substantially below the $14.65 estimated for private provision.

MEDICAL COSTS IN EXTENDED YEARS OF LIFE

The 1978 cost-effectiveness analysis included in all of its calculations the added costs of medical care during the extended years of life gained by vaccinated persons who avoided death from pneumococcal pneumonia. These costs of treating other illnesses during survivors' extra years of life varied by age and were adjusted for decreased expenditures for treating pneumococcal pneumonia. Before adjustment for decreased pneumococcal pneumonia, for example, annual medical expenditures for a person 65 years or older averaged $1,689 in 1978 dollars.

There is no consensus on whether a cost-effectiveness analysis that takes a societal perspective should include medical costs of survivors as they live out their life expectancies (61). Medical costs of survivors' additional years provide information about the cost implications for the medical care sector of the program being analyzed, and another cost-effectiveness analysis included such costs (90). However, these costs are secondary effects of vaccination and reflect the fact that people who live will continue to incur expenses, for medical care as well as for other items. There is concern that it may be misleading if not inconsistent to include one secondary and costly financial effect of vaccination, but to exclude other similar effects, such as expenses for food and clothing or improvements in production (89).

Agreement does exist on two points. One is that the effects of the medical intervention being analyzed should be followed through time. That situation does not pertain to pneumococcal vaccination against pneumonia because the disease is acute and fairly short in duration. The other point of agreement is that the factors that are appropriate to include vary if the perspective is one of a program such as Medicare. In that case, it is clearly relevant to include the present and future costs that the Program will incur because of the medical intervention. In the case of pneumococcal vaccination, those costs include the costs of

vaccination, treating side effects, and of treating other illnesses throughout the vaccinated person's life as well as savings in the costs of treating pneumococcal pneumonia.

RECONSIDERATION OF THE COST-EFFECTIVENESS RESULTS

OTA's cost-effectiveness analysis indicated that vaccination against pneumococcal pneumonia would improve health at the rate of $4,800 per healthy year of life gained across all age groups. The net gains in health were positive but small: 0.43 day for a vaccinee age 45 to 64 and 1.59 days for a vaccinee age 65 or older, for example. The net cost in 1978 dollars, which included the cost of vaccination, the cost of treating side effects, the saving in reduced costs of treating pneumococcal pneumonia, and the cost of other medical expenses in survivors' extended years, was also small: **$6.80** for a vaccinee age **45** to **64** and **$4.40** for a vaccinee age **65** or older. Expressed in terms of years, vaccination was estimated to gain a year of healthy life for a person age **45** to **64** for **$5,700** and for a person age **65** or older for **$1,000.**

If medical costs in survivors' extended years were excluded and the analysis limited to the direct effects of the vaccination, the net costs of vaccination in 1978 were estimated to be *lower* for a person age **45** to 64 **($5.65** per vaccinee or **$4,780** per healthy year gained) and to be slightly cost saving for a person age **65** or older (a saving of about $0.013 per vaccinee or $3.25 per healthy year gained).

Evaluation of the assumptions of the 1978 analysis, including available information on and the potential of the new 23-valent vaccine, has concluded that the base case assumptions are reasonable for the proportion of pneumonia caused by the vaccine types, the efficacy rate, and side effects from the vaccine. On the contrary, the low estimate seemed more likely for the incidence of pneumococcal pneumonia and for the duration of immunity. With the low estimates for these variables, health benefits would be lower and net costs higher (see table **2).** For a vaccinee **65** years or older, the lower incidence of pneumococcal pneumonia would raise the cost-effectiveness ratio to $1,300 per healthy year gained, and the shorter duration of immunity would result in **$3,000** per healthy year gained. If the lower incidence of the disease and shorter duration of immunity applied at the same time, an elderly vaccinee would gain about 0.5 of a healthy day for a net cost of **$7.60** or about **$6,000** per healthy year gained.

These figures change if allowance is made for the rise in treatment costs relative to the cost of vaccination (table 2). With the relative costs of care that prevailed in 1983, treatment costs and the savings in them from preventing pneumococ-

Table 2.—Cost-Effectiveness Results With Lower Estimates for Incidence and Duration of Immunity and 1983 Relative Prices, for Pneumococcal Vaccinees > 65 Years[a]

	Results per elderly vaccinee				
	1978 dollars			1983 dollars[c]	
Variable	Healthy days gained	Net medical costs	Net cost per healthy year gained	Net medical costs	Net cost per healthy year gained
1978 base case estimates	1.59	–$0.01	[b]	–$6.05	[b]
10 percent pneumonia as pneumococcal	1.05	3.78	$1,300	0.84	$ 291
3-year duration of immunity	0.69	5.75	3,000	4.33	2,286
3-year duration of immunity and 10 percent of pneumonia as pneumococcal	0.46	7.60	6,000	7.81	6,154

[a]All net medical costs exclude medical expenditures in survivors' extended years of life.
[b]Cost saving.
[c]$CF_{1978\ to\ 1983}$, the price of medical care rose 62.9 percent, of physicians' services 57.9 percent, and of hospital and other medical services 82.6 Percent (38).
All estimated net medical costs and net cost per healthy year gained would have cost savings if vaccination was administered under a public program (with a cost of $3.60 per vaccination) instead of private provision (with a cost of $14,65 per vaccination).

SOURCE: Office of Technology Assessment,

cal pneumonia are relatively greater. In the case of the lower incidence of pneumococcal pneumonia, the savings in treatment costs almost offset the cost of vaccination so that the net cost per elderly person vaccinated would be less than $1 for a healthy day or about **$300** per healthy year of life gained. With a shorter duration of immunity, the savings in treatment costs offset about two-thirds the vaccination cost for a net cost per elderly person vaccinated of $4.33 for **0.7** healthy day or about $2,300 per year of healthy life gained. With both a lower incidence of pneumococcal pneumonia and a shorter duration of immunity than used in the 1978 analysis, but the different relative costs that prevailed in 1983, an elderly vaccinee would gain about 0.5 of a healthy day for a net cost of about $8 or about $6,000 per healthy year gained.

RECONSIDERATION OF COSTS TO THE MEDICARE PROGRAM

The 1978 analysis concluded that the Medicare Program would incur a net cost per elderly beneficiary vaccinated of about $5 if the Program covered 100 percent of the vaccination cost. Based on the general results for elderly people, a vaccination was also expected to gain 1.59 healthy days of life.

Since the Medicare Program does not pay for the total medical expenditures of its beneficiaries, Medicare's expenditures per enrollee are a fraction of these totals. In 1978, Medicare paid 72.8 percent of hospital costs, 56.7 percent of physician charges, and 42.8 percent of the total medical expenses of their beneficiaries (27). OTA's 1978 estimate of Medicare expenditures was therefore $760 per **elderly** beneficiary. Medicare subsequently reported that it had actually spent **$864** per elderly enrollee in 1978 (83). By 1981, the most recent year available, Medicare was paying 74 percent of hospital and other medical services, 57.9 percent of physician services, and 45.3 percent of the total personal health care of aged beneficiaries.

As described above, if pneumococcal pneumonia accounted for only 10 percent of all pneumonia cases and immunity from the vaccine lasted only 3 years for elderly people, each vaccinee would gain about 0.5 of a healthy day of life. The net result for the Medicare Program of the reduced effect on pneumonia cases and of changes in relative prices of treatment and vaccination costs would be an increase in net program cost to about $5.50 to $10.50 per elderly vaccinee (table 3). If about **25** percent of elderly Medicare beneficiaries received pneumococcal vaccination (about 6.6 million people), the net cost to the Medicare Program over time in 1983 dollars would be $37 million to **$69** million to gain about 8,400 years of healthy life.

Table 3.—Estimated Net Medicare Expenditures for Pneumococcal Vaccinees > 65 Years, 1978 and 1983[a]

	Results per elderly vaccinee				
	1978 dollars			1983 dollars[b]	
Variable	Healthy days gained	Net medical costs	Net cost per healthy year gained	Net medical costs	Net cost per healthy year gained
1978 base case estimates	1.59	$5.02	$1,153	–$2.38 –$ 2.67	‘ –$ 613
10 percent pneumonia as pneumococcal	1.05	7.14	2,477	1.60 – 6.65	555 – 2,307
3-year duration of immunity	0.69	8.14	4,298	3.51 – 8.56	1,853 – 4,520
3-year duration of immunity and 10 percent of pneumonia as pneumococcal	0.46	9.21	7,258	5.54 – 10.59	4,366 – 8,345

[a] All net medical costs Include medical expenditures in survivors' extended years of life.
[b] Same price increases assumed as in table 2. Lower cost estimates were based on cost per vaccination of $9.60, and higher cost estimates on $14.65.
[c] Cost saving.

SOURCE: Office of Technology Assessment.

Chapter 3

Federal Activities Regarding Appropriate Vaccine Use

Chapter 3

Federal Activities Regarding Appropriate Vaccine Use

Since 1979, Federal activities regarding the research, development, and use of pneumococcal vaccine have related to refining information on its appropriate use and developing a vaccine with broader coverage of pneumococcal disease. In coordination with international activities, the Food and Drug Administration (FDA) promoted the development of a new 23-valent vaccine. Two institutes of the National Institutes of Health—the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Aging (NIA)—have sponsored studies on efficacy among high-risk groups. At the same time, the Centers for Disease Control (CDC) and its Immunization Practices Advisory Committee (ACIP) have evaluated the efficacy of the vaccine for certain high-risk people and made recommendations regarding its use.

TESTING AND LICENSURE OF PNEUMOCOCCAL VACCINE

Postmarketing Surveillance

Within FDA, the Office of Biologics (formerly the Bureau of Biologics) of the National Center for Drugs and Biologics is responsible for the licensure of new vaccines to ensure that manufacturers comply with established requirements governing their manufacture and distribution. Manufacturers are required to maintain and submit reports of adverse reactions experienced during prelicensure testing as part of product license applications to FDA. FDA does not currently have the authority to mandate reporting of adverse reactions by physicians. Once a product license is issued, the system for monitoring adverse reactions becomes passive. Pharmaceutical manufacturers are required to maintain reports of adverse reactions that are voluntarily submitted to them. Although manufacturers are not required to transmit those reports of adverse reactions to FDA or any other Federal agency, they must make them available to FDA inspectors during annual inspections of establishments.

The detection of adverse reactions to the marketed vaccine thus relies primarily on individuals and organizations external to FDA. For example, a problem with the manufacture of one vaccine was discovered as a byproduct of independent researchers' investigating whether pneumococcal vaccine would induce protective immunity against group B streptococcus serotype **3** (11,71). The problem was solved by subsequent changes in manufacturing procedures.

Formulation of the 23-Valent pneumococcal Vaccine

The formulation of the 14-valent vaccine was based on epidemiologic studies conducted in the United States, Europe, and South Africa. Additional knowledge gained since the licensure of that vaccine in 1977 enabled the development of a 23-valent vaccine designed to be more efficacious. The development of the new vaccine was based on the following types of new information **(62,81,82):**

1. A worldwide surveillance system of type-specific pneumococci isolated from blood and cerebrospinal fluid conducted by the World Health Organization, the Centers for Disease Control, and the laboratory of Robert Austrian.
2. Studies of cross-reactivity within types using rabbit antisera and small-scale studies of healthy adults to address specific cross-reactivity questions.

3. Reported data on the emergence of pneumococcal types and subtypes with resistance to multiple antibiotics.
4. Increased information on the stability of component antigens of the pneumococcal vaccine.
5. Limited testing of dose-response relationships on healthy adults to determine the adequacy of the 25 µg dose per antigen compared to the 50 µg dose used in the 14-valent vaccine.

Representatives of the Office of Biologics and the CDC participated as members of the World Health Organization's (WHO) Expert Committee on Biological Standardization, which developed proposals for a pneumococcal vaccine with greater worldwide applicability. That committee considered the development of a vaccine to supplement the 14-valent vaccine (i. e., a vaccine that would not include any of the types in the 14-valent vaccine) to provide protection against other pneumococcal types (92). However, there was concern that with multiple vaccines on the market, confusion might result about which pneumococcal vaccine had been administered to a patient and revaccination might occur inadvertently. The WHO Committee ultimately recommended that a single formulation be developed and accepted as an international standard (92). The Committee also recommended that new types be added to that formulation if the World Health Organization identifies them as public health problems.

WHO organized laboratories worldwide to identify the frequency with which the 83 known pneumococcal types cause pneumococcal disease. More than 13,000 isolates of blood and cerebrospinal fluid, including some from the CDC, were analyzed to provide data for the development of the reformulated vaccine (62). Based on these data, the WHO Committee proposed a new polyvalent vaccine formulation containing 23 polysaccharide types. Table 4 summarizes the formulations of both pneumococcal vaccines and the rank order of the frequency of the pneumococcal types in the specimens that were analyzed. After reviewing WHO's recommendation, FDA's Vaccines and Related Biological Products Advisory Committee concurred with the suggested reformulation of the vaccine, and FDA advised the two manufacturers licensed to sell pneumococcal vaccine in the United States of the changes (81,82).

Table 4.—Pneumococcal Types in the 14-Valent and 23-Valent Vaccines

pneumococcal type	14-valent vaccine	23-valent vaccine	Rank order in worldwide specimens
1	X	X	3
2	X	X	23
3	X	X	5
4	X	X	2
5	X	X	15
6A	X		4[a]
6B		X	4[a]
7F	X	X	7
8	X	X	6
9N	X	X	14
9V		X	11
10A		X	20
11A		X	21
12F	X	X	12
14		X	1
15B		X	19[b]
17F		X	22
18C	X	X	9
19F	X	X	10
19A		X	13
20		X	17
22F		X	16
23F	X	X	8
25F	X		24
33F		X	18

[a]The ranks for 6A and 6B are based on the frequency Of the observations for both types together.
[b]The rank for 15B is baaed on the frequency of observations for both 15B end 15C.

SOURCE: J. B. Robbins, R. Austrian, C. J. Lee, et al., "Considerations for Formulating the Second-Generation pneumococcal Capsular Polysaccharide Vaccine With Emphasis on the Cross-Reactive Types Within Groups," *J. Infect. D/s.* 148(6):1136-1159, 1963.

Testing and Licensure of the 23-Valent Vaccine

Subsequent to notification of the recommended formulation of the 23-valent vaccine by FDA, Merck Sharpe & Dohme and Lederle Laboratories both submitted product license applications for reformulated vaccines. The Lederle application included the 23-valent formulation that was agreed upon internationally. The Merck Sharpe & Dohme application, which called for a 22-valent vaccine (excluding type 33 F), was subsequently amended to conform to the recommended 23-valent formulation.

Subsequent approval of these vaccines was based on the following studies performed by the manufacturers (81,82):

- manufacturing and control tests to verify the identity and purity of the inoculum and polysaccharides and to demonstrate the consistency of production of the 23 types of pneumococcal capsular polysaccharides,
- immunogenicity studies to assess adverse reactions and antibody response to the vaccine, and
- stability studies to determine the rate of degradation of the individual pneumococcal capsular polysaccharide types.

The immunogenicity studies performed by Merck Sharpe & Dohme used three separate groups of healthy volunteers (81,82). One group of 23 adults (ages 21 to 64) was vaccinated with a 22-valent vaccine (excluding type 33f) containing 50 µg per antigen, and a second group of 29 adults (ages 21 to 64) was vaccinated with a 22-valent vaccine containing 25 µg of each antigen. Since the studies used a 22-valent vaccine, Merck Sharpe & Dohme performed a third immunogenicity study of type 33F polysaccharide alone. In that study, 25 adult volunteers (ages 22 to 29) received a single injection of 0.5 ml of the 23-valent vaccine containing 25 µg of each antigen. The results of these studies showed that the level of immune response was acceptable in all cases (a twofold or greater rise of antibodies for all pneumococcal types in 87 to 100 percent of the recipients) and that the immune response to the 25 µg dose was essentially the same as the response to the 50 µg dose.

Lederle Laboratories used a 23-valent vaccine with 25 µg per type for its immunogenicity studies (81,82). Thirty-one healthy subjects between the ages of 45 and 65 were vaccinated with the vaccine. The results showed a twofold or greater rise of specific antibody levels in 93 to 100 percent of the subjects. Another study performed by Lederle using a 14-valent vaccine containing 10, 25, or 50 µg of the 14 types showed acceptable and essentially the same immune responses for the 25 and 50 µg doses.

It is disturbing that no prelicensure immunogenicity studies for the 23-valent vaccines involved people who were older than **65** or members of other high-risk groups. The small sample sizes also raise concerns about whether the study group is representative of the larger population and whether the results can be reproduced among larger numbers of people. FDA notes, however, that recent data compiled by the CDC suggest reasonable levels of efficacy for the 14-valent vaccine (see ch. 2).

Studies of the stability of the vaccines were based in part on studies of the stability of the two manufacturers' 14-valent vaccines. Since the 23-valent vaccines were newly developed at the time the applications were submitted, studies of the long-term stability of the vaccines could not be completed and are still ongoing.

Based on the results submitted by the manufacturers, FDA determined the vaccines to be safe. The adverse reactions (e.g., swelling or soreness at the sight of the injection, low-grade fever) observed in the recipients were not considered serious (81,82).

FDA approved PNEUMOVAX-23 (Merck Sharpe & Dohme) on June 30, 1983, and PNU-IMUNE 23 (Lederle Laboratories) on July 15, 1983. The approved indications for use of the vaccine specified on the package insert follow the recommendations for use of the 14-valent vaccine that were made by the ACIP in 1981 (see below).

RESEARCH ON pneumococcal VACCINE

The National Institutes of Health has been a major sponsor of pneumococcal vaccine research through NIAID and NIA. NIAID initiated a program to develop a polysaccharide pneumococcal vaccine in 1967. Its involvement in the early stages of pneumococcal vaccine development included providing support for Robert Austrian of the University of Pennsylvania, recognized as the leader in the development of this vaccine (85).

Two major studies of the efficacy of pneumococcal vaccine in the United States were also conducted under contract to NIAID: one that involved more than 13,000 essentially healthy

volunteers at the Kaiser-Permanante Medical Center in San Francisco, and the other of more than 1,300 long-term institutionalized patients at the Dorothea Dix Hospital in Raleigh, N.C. Neither of these studies demonstrated significant differences between vaccine and placebo recipients in the attack rates of radiographically documented pneumonia. During the Kaiser-Permanente trial, the incidence of pneumococcal pneumonia was very low. The results from Dorothea Dix Hospital were interpreted as suggesting that either the efficacy of the vaccine was low for the groups studied or the attack rate of pneumonia due to vaccine-susceptible pneumococci was very low (13).

NIAID is currently supporting basic research into the development of conjugated polysaccharide vaccines (coupling polysaccharide antigens to protein carriers). It is hoped that these vaccines will achieve greater efficacy for children and people with immunological deficiencies **(30).** Numerous clinical trials in infants and young children have been conducted. Although the initial work in the development of conjugated vaccines is being performed with *Hemophilus influenza* type b, the basic research is expected to be relevant to the development of other conjugated polysaccharide vaccines, such as pneumococcal vaccine.

NIAID has supported a large number of studies of the immunogenicity of pneumococcal vaccine through a contract with Gerald Schiffman of the State University of New York, who conducts assays to measure the levels of antibody stimulated by pneumococcal vaccine (44). Through that contract, NIAID is supporting the clinical trial of pneumococcal vaccine in the Veterans Administration (see ch. 2).

NIA has expressed concern about the absence of acceptable data on the effectiveness of pneumococcal vaccine for elderly people. Proceedings of a 1981 conference cosponsored by NIA and NIAID note that there are no published randomized placebo-controlled trials that conclusively show the efficacy of the vaccine in elderly people (65). NIA is supporting a study by Bentley and Schiffman, which is extending their preliminary findings on the immune response of elderly people to pneumococcal vaccine.

Concluding that more definitive studies were needed to determine the efficacy of pneumococcal vaccine in elderly people, NIA together with NIAID in 1982 issued an announcement calling for research and grant applications on the subject. The announcement specifically called for studies on the efficacy of pneumococcal vaccine in various subpopulations of the elderly and on the presence of nonvaccine serotypes of pneumococci in the immunized and nonimmunized elderly (84).

SURVEILLANCE ACTIVITIES

Since licensure of pneumococcal vaccine in 1977, CDC's activities have related to refining information on the vaccine's effectiveness and appropriate use for specific high-risk groups. The only surveillance system for pneumococcal infection in the United States is the CDC's Pneumococcal Surveillance System in the Center for Infectious Disease, Division of Bacterial Diseases. Since 1978, a group of hospitals (currently 37) have submitted subcultures of all pneumococci isolated from blood and cerebrospinal fluid to the CDC for serotyping (14). This sample of hospitals was nonrandomly chosen to include hospitals of different types in 22 different States. Most of the hospitals (25 of the original 37) were also participants in the CDC National Nosocomial Infection Study **(15).**

The original purpose of the pneumococcal Surveillance System was to examine the distribution of pneumococcal types and any change in that distribution with vaccine use. CDC data indicate that no shift in the distribution of pneumococcal serotypes has occurred since the introduction of the 14-valent vaccine (15). The CDC has also used information from its Surveillance System to estimate the type-specific efficacy of the 14-valent vaccine for elderly and other high-risk people (16). The methodology entailed comparing pneumococcal types associated with disease in vaccinated and unvaccinated people (see ch. 2).

RECOMMENDATIONS FOR USE OF PNEUMOCOCCAL VACCINE

The ACIP, an advisory group to the Public Health Services, is responsible for making recommendations on the use of new vaccines and for periodically revising recommendations on existing vaccines. ACIP members are selected from nominations made by professional and academic societies and represent experts in relevant disciplines (e.g., epidemiology, microbiology, public health, immunology) **(20).** Representatives of the FDA Office of Biologics and NIAID serve as ex-officio members. The ACIP also has liaison members from professional organizations such as the American Academy of Pediatrics and the American Medical Association.

The ACIP has issued two sets of recommendations on the use of pneumococcal vaccine: one in January 1978, shortly after a 14-valent vaccine was licensed, and the second in August 1981. The ACIP reviewed additional information regarding pneumococcal vaccine in February 1984.

The 1978 and 1981 statements reflected the Committee's sense that it had insufficient information about vaccine efficacy. The 1978 recommendations clearly stated that because of insufficient information on the efficacy of pneumococcal vaccine, " . . . definitive recommendations for its use cannot be formulated at the present time" (59). However, they also concluded that pneumococcal vaccine induces satisfactory antibody response in persons over 2 years of age, antibody titers are likely to remain high for several years, and the potential exists for reducing pneumococcal disease in the United States through use of the vaccine (59).

The 1981 statement also noted that available data were not yet sufficient for conclusive recommendations. Although it included a statement that the 14-valent vaccine had been shown in selected young healthy populations to reduce the incidence of pneumonia caused by types contained in the vaccine, the statement went on to say that the data upon which these findings were based came from adults who were at increased risk of disease but were not chronically ill **(58).**

Table 5 compares the two sets of recommendations for six groups. Neither list includes elderly people per se. This omission contrasts with the vaccine labeling, which includes people 50 years or older, whether or not they have underlying medical conditions.

The ACIP does issue unequivocal statements about the use of a vaccine when sufficient data supporting those recommendations are available. For example, in its 1982 recommendations on influenza vaccine, the ACIP "strongly" recommended the vaccine for all older persons, particularly those over age 65, and for five other high-risk groups **(37).** Thus, the tone of the 1978 and 1981 pneumococcal vaccine recommendations is a reflection of the ACIP's perception that definitive evidence on the efficacy of pneumococcal vaccine did not exist at that time.

NATIONAL OBJECTIVE FOR 1990

The 1979 Surgeon General's draft report on health promotion and disease prevention established reduction in the number of premature deaths from pneumonia and influenza as a primary goal (88). The goals established in 1979 were reaffirmed when a series of "1990 Immunization Objectives" were published in 1983. Among the objectives to implement that goal was one regarding pneumococcal vaccine:

> By 1990, at least 60 percent of high-risk populations., as defined by the ACIP. should have received vaccination against pneumococcal pneumonia; at least 50 percent of people in populations designated by the ACIP should be immunized within 5 years of licensure of new vaccines for routine clinical use.

This objective was given a *medium priority* for Federal activity and assigned to the CDC for implementation. The working groups that developed this and other national objectives foresaw their attainment through the active participation of or-

Table 5.–Recommendations of the Immunization Practices Advisory Committee (ACIP), 1978 and 1981

Target groups	1978	1981
Persons older than 2 with splenic dysfunction or anatomic asplenia (absence of spleen)	Should benefit from being immunized	Should benefit from immunization. Failures have been reported, perhaps due to impaired antibody responses, but vaccine is recommended because patients are known to be at high risk of developing fatal bacteremia
Persons older than 2 with certain chronic illnesses associated with a greater risk of pneumococcal disease	Might benefit from immunization. Because risk and case fatality increase with age, benefits of vaccination should increase with age	Should be considered candidates for vaccination. Vaccine may be increasingly beneficial as these patients grow older because of increased fatality rate from pneumococcal infections. Vaccine efficacy in these groups needs further evaluation
Healthy populations	Mass immunization is not currently recommended	Insufficient data to formulate a recommendation on routine use of the vaccine for the general population, including the elderly. This should not preclude health care providers from immunizing healthy persons whom they believe may benefit
Closed populations such as those in nursing homes or residential schools when there is an acute outbreak or high rate of endemic pneumococcal disease	Immunization of the entire closed population might be an effective control measure	Vaccination of the entire closed population should be considered
Populations living in areas where there are localized outbreaks of pneumococcal disease caused by types represented in the vaccine	Selective immunization of groups in the community epidemiologically believed to be at particular risk may be useful	Selective immunization of those at high risk should be considered
Patients at high risk of influenza complications (particularly pneumonia)	Consideration should be given to vaccinating such patients	pneumococcal and influenza vaccines can be given at different sites at same time without increased side effects
Pregnant women	Theoretically should not be harmful but in view of recommendations that unnecessary drugs and vaccines should not be given during pregnancy, pneumococcal vaccine should only be used when there is substantial risk of infection	Safety for pregnant women has not been evaluated. Should not be given during pregnancy unless risk of infection is substantially increased
Second or booster doses	There appears to be no booster effect with additional doses	Should not be given at this time because of marked increase in adverse reactions with reinfection of pneumococcal vaccine

SOURCES: "Recommendation of the Immunization practices Advisory Committee (ACIP): pneumococcal Polysaccharide Vaccine," *Morb. Mortal.* Weekly *Rep.* 30:410-419, 1981; and "Recommendation of the Public Health Service Advisory Committee on Immunization practices: pneumococcal Polysaccharide Vaccine," *Morb. Mortal* Weekly *Rep.* 27(4):25-31, Jan. 27, 1978.

ganizations and interested parties at all levels of Government and within the private sector (41).

At the time the objective was set, it was noted that baseline data for measuring progress toward the objective were not available. Periodic sample surveys were noted as the source of data for future assessment of whether or not the objective was being approached (86). The CDC has at least two potential sources of information: the Annual Immunization Survey and Biologics Surveillance. Through the Bureau of the Census, the CDC collects information on the use of vaccines in its annual U.S. Immunization Survey. Using a random sample of 35,000 housing units, the survey reports the percent of the population that have had rubella, measles, diphtheria-tetanus-pertussis, poliomyelitis, mumps, and influenza vaccinations. Although the U.S. Immunization Survey has not covered pneumococcal vaccination, the CDC plans to include it in the survey beginning this year **(21).** However, because of the small numbers of people who receive pneumococcal vaccine each year, the survey may not be able to provide statistically significant data about use in the target population.

The CDC also compiles "Biologics Surveillance" on a semi-annual basis. This document lists sales net of returns for the major vaccines marketed in the United States by three or more manufacturers. Although data on pneumococcal vaccine have not been included to date, they maybe added in the future. Since only two manufacturers market pneumococcal vaccine in the United States, this step would require special arrangements between the CDC and the manufacturers.

Despite the existence for several years of the objective of vaccinating **60** percent of the target group, the CDC has only recently begun to collect baseline data and has not actively promoted vaccine use. This passive posture has been consistent with uncertainty regarding efficacy (33), appropriate target groups, and the indefinite recommendations of the ACIP. However, at its recent meeting, the ACIP began to reconsider pneumococcal vaccine and expressed an intention to change substantially its previous statement. In light of data that suggested efficacy of about **60** to **70** percent for elderly people and some other high-risk groups (see ch. 2), the Committee stated a desire to develop more definite recommendations for specific target groups. It also charged a subcommittee to prepare draft recommendations for the April **1984** meeting.

Chapter 4

Medicare Coverage of pneumococcal Vaccine

Chapter 4

Medicare Coverage of Pneumococcal Vaccine

As a result of the enactment of Public Law 96-611, in December 1980 pneumococcal vaccination became a reimbursable service under the Medicare Program, effective July 1, 1981. Pneumococcal vaccination thus became the first and to date the only preventive service paid by Medicare. With the exception of pneumococcal vaccine and its administration, the Social Security Act specifically excludes payment for preventive immunizations.

Bills to extend coverage to pneumococcal vaccine were first introduced into Congress in fall 1979. Subsequent consideration of the legislation focused on the fact that Medicare was then paying for the treatment of pneumococcal pneumonia but not for its prevention and that the vaccine had few and relatively minor side effects (60). There was also substantial interest in the financial implications for the Medicare Program. Besides the OTA cost-effectiveness analysis, a study by the Congressional Budget Office (CBO) provided relevant information. The CBO study concluded that Medicare would incur additional net costs during the initial years of coverage, but net reductions in future years. [1]

[1]The analysis was conducted including and excluding survivors' medical costs.

Since 1980, two other vaccines have been considered for Medicare coverage: hepatitis B vaccine for end-stage renal disease patients and influenza vaccine. Coverage of hepatitis B vaccine is included in the House and Senate reconciliation bills now before Congress. Inclusion of influenza vaccine was considered along with pneumococcal vaccine in 1980 and with hepatitis B vaccine in 1983. But despite the stronger statements of the Immunization Practices Advisory Committee (ACIP) regarding the advisability of influenza vaccine for elderly people (58), influenza vaccination has not become reimbursable under Medicare. Like payment of pneumococcal vaccine, the exclusion of influenza vaccination and serious consideration of hepatitis B vaccine may hinge on the implications for Medicare costs. Although hepatitis B vaccine is more expensive per dose, the Program costs of paying for hepatitis B vaccine would most likely be lower than for influenza vaccine because coverage would be limited to a much smaller number of beneficiaries, end-stage renal disease patients, rather than all aged or chronically ill ones.

IMPLEMENTATION OF MEDICARE COVERAGE

At the same time that Medicare coverage of pneumococcal vaccine was being enacted in late 1980, there was discussion in the administration about rescinding that measure. Concerns were raised about the efficacy of the vaccine and, in the early part of 1981, about the additional costs to Medicare during initial years of coverage (60). Efforts to rescind coverage were defeated in the summer of 1981.

In implementing coverage of pneumococcal vaccination, Medicare applied the same procedures as for other services covered under Part B. The Bureau of Program Operations in the Health Care Financing Administration (HCFA) notified the carriers through changes in the Carrier Reimbursement Manual (94). The carriers in turn were responsible for adjusting their systems for paying claims. Presumably special procedures were

necessary for pneumococcal vaccination because it is not subject to the deductibles and coinsurance that usually apply to **Part B** services. Although information is not available on how all of the carriers handled the change, the carrier[2] for the Commonwealth of Virginia assigned a separate procedure code to pneumococcal vaccination (75). After consulting the *American Druggist Blue Book,* that carrier has set the reimbursable charge for vaccination at **$9.60: $7.50** for the vaccine, $0.10 for the syringe, and $2 for physician time (the rate paid for injections) (17).

In January 1982, the Social Security Administration included information about coverage of pneumococcal vaccination as a "stuffer" with Social Security checks. This medium is commonly used to inform beneficiaries about notable Program changes. The notice thus appeared **6** months after coverage had begun. More importantly, it occurred in January, after the fall, the peak of public and medical concern about respiratory diseases, such as pneumonia and influenza, and it did not mention diseases, such as pneumonia, that might be prevented by the vaccine (see fig. 1).

[2]Carriers **throughout the United States set reasonable charges,** implement changes, and pay claims for Medicare Part B services.

Figure 1 .—Announcement to Beneficiaries of Medicare Coverage of Pneumococcal Vaccine, January 1982

An important message for beneficiaries who plan to work in 1982

Beginning January 1, 1982, you can earn more and still receive all your Social Security checks.

- If you are now 65 or older, or you will reach 65 in 1982, you can earn $6,000 and still receive all your checks, If your total yearly earnings go over $6,000,$1 in benefits may be withheld for each $2 of earnings above $6,000.
- If you are under 65 all of 1982, you can earn up to $4,440 and still receive all your checks. If your total yearly earnings go over $4,440,$1 in benefits maybe withheld for each $2 of earnings above $4,440.

In 1981, the annual exempt amounts were $5,500 for people 65 and over and $4,080 for people under 65.

If you worked and earned more than the annual exempt amounts in 1981 while receiving benefits, you must complete an annual report of earnings by April 15, 1982, unless you were 72 or older all year.

Note: Beginning with the month you reach age 72, you get your full check each month no matter how much you earn.

Different rules apply to people **receiving** Social Security disability or **SSI payments** if they work. Please see other side.

If you receive Social Security disability or SSI payments, you must report *all* work, no matter how much you earn. (If you are a payee for someone receiving these benefits, you must report for him or her.)

You can make your report by phoning, writing, or visiting any Social Security office. Look up "Social Security Administration" in the phone book to find the office nearest you.

pneumococcal vaccine shots

pneumococcal vaccine shots are now a covered service under Medicare. Ask your doctor's advice about your need for this vaccine.

Medical insurance deductible

Starting in 1982, the annual deductible for the medical insurance part of Medicare is $75, instead of $60.

U.S. Department of
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PNEUMOCOCCAL VACCINATION UNDER MEDICARE PAYMENT BY DIAGNOSIS RELATED GROUPS

Although Medicare has historically paid hospitals for the costs that they have incurred, a new system is being implemented that bases payment on the costs set in advance for diagnosis related groups (DRGs). HCFA has interpreted Public Law 98-21, which mandated DRG payment, and Public Law 96-611, which covered pneumococcal vaccination, as permitting Medicare to pay hospitals separately from the DRG system for pneumococcal vaccination. A hospital maybe reimbursed for the reasonable costs of providing pneumococcal vaccination to patients, including inpatients, who are Part B beneficiaries. The rationale is that DRG payment applies to Part A services, while pneumococcal vaccination is covered only as a Part B service. Public Law 98-21 specifically excluded physician services to hospital patients from the DRG system. Besides physician services, only two other services are covered under Part B but not Part A and hence are excluded from the DRG limits for payment for inpatients: pneumococcal vaccination and ambulance service to transfer patients from one prospectively paid hospital to another (35).

HCFA gave public notice of these decisions in the September 1, 1983, statement in the Federal Register on interim final regulations for prospective payment to hospitals. Although that notice did not include the specific implications for pneumococcal vaccination, a subsequent notice to intermediaries in October 1983 listed pneumococcal vaccination and ambulance transfer of patients as exceptions to DRG payment (29).

Although HCFA's decision was based on statutory language, the resulting payment procedure has avoided creating a financial incentive for a hospital to not provide pneumococcal vaccination. If pneumococcal vaccination were included in DRGs (as other preventive technologies are), its use would add to the hospital's costs, but not to its revenues (48). This situation is important for pneumococcal vaccination because the hospital has been suggested as an institution through which pneumococcal vaccination could be provided (22). On the basis of the percentage of patients with pneumococcal pneumonia or bacteremia who were hospitalized within the previous 3 years for any cause, Fedson has estimated that vaccinating certain patients on discharge from their previous hospitalization could avoid 10 percent of hospital admissions for all pneumonia.

ESTIMATED USE OF PNEUMOCOCCAL VACCINE

HCFA's present data systems do not permit the development of aggregate data at the national level on Part B services, such as pneumococcal vaccination (76). It is, however, an identifiable line item (a separate payment record) that the carriers submit to HCFA. New procedures are now being implemented to permit national samples of such services to be derived. HCFA is requiring all carriers to use a standard set of codes by the end of 1984 and to notify HCFA if they create new ones. Starting in July 1984, HCFA will sample the standardized data available on Part B services, and by July 1985, data from all carriers will be on the system (93).

Two sets of information do pertain to the use of pneumococcal vaccine: sales of the two vaccine manufacturers and IMS America data on physician mentions of the vaccine in the National Drug and Therapeutic Index (NDTI) and on purchases by hospitals and drug stores. The data indicate that at the most 35 percent of high-risk people have received the vaccine.

Manufacturers report sales of about 11.1 million doses of pneumococcal vaccine, net of returns, since 1978, when the first vaccine was marketed (table 6). The precise number of people at high-risk of pneumococcal disease is unknown. An approximation, however, are the people at high risk of influenza because of certain chronic conditions: diabetes, kidney disease, asthma, emphysema, tuberculosis, bronchitis, heart condition, rheumatic heart condition, hypertension, or

Table 6.—Total Sales of Pneumococcal Vaccine, Net of Returns, 1979-83

Year	Number of doses
1978	2,964,000
1979	1,565,605
1980	1,774,135
1981	2,283,240
1982	1,152,510
1983	1,313,105
Total	11,052,595

SOURCE: Unpublished data, Lederle Laboratories and Merck Sharpe & Dohme, January and February 1964.

hardening of the arteries. According to responses from a household survey, about 32 million people in the United States had such chronic conditions in 1982, including 12 million 65 years or older (table 7). If that population is indicative of the target group forpneumococcal vaccine, that vaccine has been sold for about 35 percent of the high-risk population. Including all elderly people would add 13.5 million people to the target group (87) and reduce the coverage of doses sold to about 24 percent. Including people 50 to 64 years, in accordance with the Food and Drug Administration's approved labeling, would add an additional 10.4 million to the target group for a coverage rate of 20 percent.

All of these percentages should reconsidered high estimates of use because they relate to doses sold rather than doses used. Doses sold include unknown quantities of inventories and of wastage. Since the labeling and ACIP recommend against reimmunization, it is unlikely that many people have received more than one dose.

Additional information on vaccine use comes from the NDTI of IMS America, Ltd. That survey asks a sample of physicians from a panel to indicate the pharmaceutical products related to their physician-patient encounters, regardless of location. The survey indicated that private physicians (excluding those in health maintenance organizations) had used only about 1.1 million doses of pneumococcal vaccine from 1979 to 1983 (table 8). Even after allowance for a sampling error of about 32 percent because of the small sample size (63), the figure differs markedly from manufacturers' sales, and there is no apparent explanation for the great disparity. IMS America data on purchases by hospitals and drug stores add fewer than 1 million doses (table 9). However, this data base has generally been considered more useful for qualitative as opposed to quantitative information on physician practice (40).

The NDTI data indicate several interesting patterns of use. As one would expect, primary care physicians (general or family practitioners, internists, and pediatricians) accounted for almost all of the vaccine mentions (table 10). Similarly, physicians age 50 to 64, who are most likely to have elderly patients, accounted for over half of the vaccine mentions (table 11), and patients 65

Table 7.—Persons in the United States With Certain High-Risk Conditions by Age, 1982

Years of age	Number with conditions (thousands)	Percent of total population in that age group
18-24	1,530	5
25-44	6,030	9
45-64	12,448	28
> 65	12.031	47
Total	32,039	19

[a]Conditions include diabetes, chronic kidney disease, asthma, emphysema, tuberculosis, chronic bronchitis, or chronic heart condition such as heart attack, rheumatic heart condition, high blood pressure, or hardening of the arteries.

SOURCE: Unpublished data, "U.S. Immunization Survey, 19S2," Centers for Disease Control, Division of Immunization, Atlanta, January 1984.

Table 8.—Physician Mentions of Pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTI), 1979-83

Year	Number of mentions (thousands)	Percent of total
1979	160	15
1980	255	23
1981	289	26
1982	218	20
1983	170	16
Total	1,092	100

SOURCE: IMS America, Ltd., Rockville, Md., unpublished data, February 1984.

Table 9.—IMS America Data on Pneumococcal Vaccine Purchased by Hospitals and Drug Stores, 1978-82 (thousands)

	Hospitals		Drug stores	
Year	Number of doses	Dollars	Number of doses	Dollars
1978	74.8	$1,840	204.0	$ 5,012
1979	42.2	1,081	75.2	1,835
1980	46.1	1,192	65.8	1,578
1981	48.9	1,241	126.5	3,101
1982	38.6	961	105.1	2,550
Total	250.6	$6,315	576.6	$14,076

SOURCE: IMS America, Ltd., Rockville, Md., unpublished data, February 1984.

Table 10.—Physician Mentions of Pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTI) by Specialty, 1979-83

Specialty	Percent
General or family practitioners	54.3
Internists	28.2
Osteopaths	6.3
Allergists	3.7
Pediatricians	3.0
General surgeons	2.7
Cardiologists	1.1
Gastroenterologists	0.3
Urologists	0.3
Ear, nose, and throat specialists	0.2
Total	100.0[a]

[a]Total may not add to 100 percent because of rounding

SOURCE IMS America, Ltd., Rockville, Md, unpublished data, February 1984

Table 11 .—Physician Mentions of Pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTl) by Physician Age, 1979-83

Age	Percent
20-39	14
40-49	20
50-64	52
> 65	14
Total	100

SOURCE IMS America, Ltd., Rockville, Md, unpublished data, February 1984,

years or older accounted for 60 percent (table 12). Almost 90 percent of the vaccine mentions *were* associated with no specific diagnosis (table 13). This result may reflect that healthy people were receiving the vaccine or may simply bean artifact of the *survey* procedure,

Data from a large prepaid group practice in California are consistent with the sales reported by manufacturers. From 1979-83, the group used about 42,000 doses for its members, who consisted of about l10,000 people 65 years or older (70). Data are not available on the characteristics of the people who received the vaccine. If the members had the same rate of chronic conditions by age as the general population, which may be a high estimate, the group had vaccinated about 16 percent of its high-risk members or 13 percent if all members over 65 years are also included. That percentage would be higher to the extent that fewer high-risk people were represented in the membership,

It is difficult to identify a vaccine whose use may be compared with that of pneumococcal vaccine. Influenza vaccine is intended for similar

Table 12.—Physician Mentions of Pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTI) by Patient Age, 1979-83

Age	Percent
0-2	2
3-4	1
5-24	7
25-44	4
45-64	25
65-99	61
Total	100

SOURCE: IMS America, Ltd , Rockville, Md., unpublished data, February 1984

Table 13.—Diagnoses Associated With Physician Mentions of pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTI), 1979-83

Diagnoses	Percent
pneumococcal immunization	**64.7**
Immunization mixed	**24.2**
Rhinitis allergic	**1.1**
Chronic obstructive pulmonary disease	0.9
Surgery after spleen	0.8
Influenza inoculation	0.6
Allergic disorder	0.5
Emphysema without bronchitis	0.5
Perennial rhinitis	0.5
Fibrosis of lung	0.5
Disease of the mitral valve	0.5
Otitis media	0.5
Bronchiectasis	0,4
Fibroid disease of lung	0.4
Pneumonia unspecified	0.4
Hay fever with asthma	0.4
Congestive heart failure	0.2
Sinusitis allergic	0.2
Asthma allergic	0.2
Stenosis of aorta	0.1
Other	2.7
Total	100.0[a]

[a]Total may not add to 100 percent because of rounding

SOURCE IMS America, Ltd , Rockville, Md., unpublished data, February 1984

high-risk groups, primarily adults, but since it should be given every year, coverage of the target group (about 20 percent) is indicated by annual use rather than cumulative use over several years. Existing data on other vaccines pertain to those recommended for universal childhood immunization, **a** situation quite different from the selective, primarily adult use of pneumococcal vaccine. Of all the childhood vaccines, the case of mumps vaccine is the most similar to pneumococcal. By 1973, about 35 percent of the preschool population (1 to 4 years) had received mumps vaccine, which was first marketed in 1968 (21), The initial statement by the ACIP was vague, and the medical community did not promote mumps vaccine

because it did not consider the disease severe (66). Government funding for mumps vaccine began in 1973 (32), but doses sold jumped 18 percent after a multiple vaccine containing mumps, measles, and rubella was marketed in 1971 (21).

A striking feature of sales of pneumococcal vaccine is the spurt in 1981 followed by a sharp decline in 1982 (table 6). The manufacturers reported no increase in returns of vaccine during 1982. That NDTI data, which pertain to physician use rather than sales, have the same pattern suggests that the phenomenon applied to use of the vaccine, although the changes in use may have been less dramatic.

The manufacturers had undertaken public service announcements or advertising in the medical and lay publications to promote the vaccine. They reported no substantial change in expenditures between 1981 and 1982, but more may have been channeled to lay publications and less to direct promotion to physicians. The 1981 ACIP statements mentioned that pneumococcal and influenza vaccines could be administered at the same time, but the use of pneumococcal vaccine had already been much heavier in the fall, when influenza vaccine is given, than at other times of the year (table 14). Medicare's notice to beneficiaries of coverage did not appear until 1982.

The most likely explanation for the increase in 1981 was the start of Medicare coverage of pneumococcal vaccine. Although the level of promotional activities may not have changed, in 1981 the material included as a prominent feature the fact that Medicare would pay for the vaccine and its administration **(26).** In general, studies have found that the use of medical services is greater when patients bear lower costs (79). The Rand Health Insurance Study has found that this pattern applied to preventive services, which consist mostly of childhood care and prenatal services (57). However, studies specifically of immunizations have been inconsistent, with many confounding variables (79).

If Medicare coverage accounted for an increase in sales and use during 1981, that effect was transitory and not sustained even into 1982. Part of the swings may have been changes in inventories. pneumococcal vaccine does not expire for 2 years. Physicians and other providers may have ordered heavily in 1981, anticipating much greater demand because of Medicare coverage. If substantial supplies remained at the end of the year, they may have carried them over to 1982 and decreased their 1982 orders.

It is also possible that the physicians who were receptive to prevention and to pneumococcal vaccine administered it to their patients during the initial years after the vaccine became available (23). Since reimmunization is not advised, this hypothesis would predict that use would soon decline, as it did in 1982.

None of these data applies specifically to use by Medicare beneficiaries. Their use may have ranged from 5.3 million to 6.6 million vaccinations based on 20- to 25-percent use rates respectively. (The 35-percent use rate does not apply because it was derived by excluding people over age 65 who did not have certain high-risk conditions.) Assuming that people 65 years or older have received 60 percent of the vaccinations (NDTI data, table 12) also results in an estimate of 6.6 million vaccinations. At a cost of $9.60 per vaccination for 6.6 million, Medicare would have spent about $175 million on vaccination cost alone, and beneficiaries would have gained about 8,400 additional years of healthy life (see ch. 2). With savings in the cost of treating pneumococcal pneumonia and survivors' additional medical costs over time, the net Program cost in 1983 dollars would range from $37 million to $69 million.

Table 14.—Physician Mentions of Pneumococcal Vaccine in the National Drug and Therapeutic Index (NDTI) by Month, 1979-83 (percent)[a]

Month	1979	1980	1981	1982	1983
January	5	0	3	13	5
February	0	2	3	5	4
March	6	3	5	7	0
April	0	0	2	0	3
May	0	3	0	4	12
June	3	0	0	2	4
July	2	0	2	0	0
August	4	3	7	3	0
September	9	17	9	7	16
October	16	36	30	33	32
November	33	20	20	17	17
December	22	16	18	8	7
Total	100	100	100	100	100

[a]Totals may not add to 100 percent because of rounding.

SOURCE: IMS America, Ltd., Rockville, Md , unpublished data, February 1984

Appendix A

Acknowledgments

Appendix A

Acknowledgments

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